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bane and blessing

In 1895 Roentgen discovered roentgen rays and it was soon found that this form of radiation, like ultraviolet rays from the sun, produced keratotic, precancerous lesions of the skin. In 1896 Becquerel discovered the radioactivity of uranium and found that these rays, like roentgen rays, ionized the air. In 1898, the Curies discovered radium and its radiations.

For their discoveries, in 1903, the Nobel prize in physics was awarded jointly to Becquerel and the Curies. In 1905, Pierre Curie before the Academy of Science of Stockholm, in his Nobel lecture, spoke of the consequences of the discovery of radiant energy: fundamental principles of mechanics had been profoundly modified; a new source of chemical energy had been hypothesized; the key had been found to geological and meteorological phenomena previously unexplained; biological effects had been discovered, both beneficial and harmful. Could this new knowledge be so limited as to serve only the Good, or would it also serve Evil? In criminal hands radiant energy might become very dangerous. Was humanity ripe enough to profit? Nobel's own discoveries of powerful explosives, although a terrible means of de-

struction, had enabled man to perform constructive work. Curie was of the opinion that humanity would obtain more good than evil from the new discoveries. He was a greater prophet than he knew; for although radioactivity is now the most powerful potential agent of suffering and mass destruction the world has ever known, it is also a blessing of modern man. It has eased pain, parried death, and saved the lives of countless cancer sufferers.

Today chemist, physicist, biologist, mathematician, physician all work together in obtaining fundamental knowledge concerning the structure of the atom and the nature of radiant energy, and in applying this knowledge to the practical use of mankind, including the diagnosis and treatment of cancer.

The use of radiation in diagnosis and treatment has now extended beyond the application of roentgen rays and radium. Use of isotopes, of particle-accelerating beams generated at multimillion volts, of precision targeting, of target rotation, of super-voltage roentgen-ray apparatus, of techniques to increase cellular radiosensitivity—all contribute toward the effectiveness of curative and palliative radiation therapy in neoplastic disease.



Cover

The two-million volt x-ray machine in the Radiation Therapy Department of the Hospital for Joint Diseases, New York City.

NEWSLETTER

MARCH, 1953

HERE AND THERE IN RESEARCH

Ackerman (Wash. U.) and other authorities on pathology have been conducting a guessing game for the benefit of the nation's pathologists for the past few years. Ackerman and other "fall guys" receive slides from pathologists and, at regional meetings of pathologists, tell their diagnosis. Argument and abuse by the audience are invited -- and always are forthcoming. The "game" has sharpened pathologists' ability to identify common and uncommon tumor types.

Scharrer (Col. U.) is one of several investigators introducing a new concept of pituitary function. Her work, in large Latin-American cockroaches, indicates that the posterior pituitary may not synthesize hormones but merely be a reservoir for hormones produced in the hypothalamus.

Lyman (Harvard U.) has virtually stopped all growth in hamsters by making them hibernate. The animals hibernate at near-freezing temperatures. Their respiration and pulse drop to about one-fiftieth normal, blood becomes jelly-like, and even teeth (which continually are being ground down and regenerated) fail to grow. Next step is to see what happens to induced and transplanted tumors in the hamster's pouch.

Suspenseful are the experiments of De Bruyn (Chicago U.) who has incorporated radioactive tritium into flavine dyes and is now testing it as a possible anticarcinogenic agent. The flavine settles exclusively in the nuclei and preferentially in dividing cells. The tritium has rays so short that they do not spill over from the nucleus to the cytoplasm. Theoretically, it's a good problem.

The Silberburgs (Wash. U. and St. Louis City Hosp.) have raised the incidence of leukemia and hyperplastic adrenals in one mouse strain from 2 to 25 per cent with homologous transplants of pituitaries. The animals

are castrated and about four pituitaries from young brother and sister mice are transplanted under the chest skin. The results may be due to hyperestrogenation caused by pituitary (ACTH) stimulation of the adrenal cortex.

During the last two years Richardson (formerly U. of Ore. and now at Memorial Hosp., N. Y.), Griffin (Stanford U.), and the Millers (Wis. U.) have found that two carcinogens (methylcholanthrene and azo dyes, for instance) applied simultaneously to the same animal usually resulted in no cancers at all. Richardson has made some preliminary observations indicating that the two cancer causers somehow erode areas of the adrenal cortex -- in effect, a chemical adrenalectomy. Griffin now has noted that hypophysectomized rats fed azo dyes don't get liver cancer -- but if they are given gonadotropin they do undergo extensive liver degeneration and cirrhosis.

Jones (U. of Pa.) has demonstrated again that bone-marrow injections protect against lethal radiation -- after exposure. In rat experiments, 75 per cent of untreated irradiated controls died, as compared with 30 per cent of the treated animals. One thousand roentgens was the dose. Significant protection was lost at 1,200 r.

Wissler (Chicago U.) has produced antiserums, twice as strong as any heretofore reported, against some animal tumors. Some degree of prevention has been achieved. By impregnating the antibodies with radio-fluorescein, much of the guesswork may be eliminated from observations.

Hauschka (Institute for Cancer Research) continues to find polyploid cancer cells readily transplantable to several mouse species. Diploid cells, on the other hand, continue to be transplantable only to the strain of origin.

Stowell (Kansas U.) and Homburger and Fishman (Tufts) have checked about a score of potential blood tests for cancer and, so far, have found none of practical value.

Scott and associates (Hopkins) now have done six human hypophysectomies for advanced prostatic cancer. The patient to survive the longest has lived eight months with significant remission. The first case died of a pulmonary embolus five months after operation -- and post-

(Continued after page 88)

Cancer

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Keeping up

Radium Therapy in Cervical Cancer

The technique, dosage, and results of treatment of cancer of the cervix uteri with interstitial radium at the Gynecological Tumor Clinic of the Rhode Island Hospital are discussed, and on the basis of experience there it is concluded that the method is a valuable one and deserves further exploration. In the last 321 consecutive primary cases of cervical cancer treated between the years 1936 and 1944, there were 146 five-year survivals, or 45.5 per cent. Needles used are the French or Belgian type, carry small amounts of radium, 2 to 3 mg. element, and are filtered by 0.5 mm. of platinum. They can be left in the tissues for protracted single treatment up to seven days. A wide and fairly uniform distribution of the needles about and in the tumor as well as individualization of treatment are possible. A variable number of needles are used according to the size of the growth. The lateral parametria or the lymph-node area must be treated by other means, such as external deep roentgen-ray therapy. Roentgen-ray therapy is given before radium only in the advanced or badly infected case. In the earlier cases, or when infection is not a factor, radium treatment first is preferred, using external roentgen-ray radiation six to eight weeks later. Calculation of dosage in terms of a universal standard, the gamma roentgen, will help greatly in permitting more scientific application and distribution of radium sources. If dosage at certain vital points in and

about tumors or at certain vulnerable points in normal tissues can be determined, radium sources will be better placed to destroy cancer effectively and to avoid overdosage and destruction of normal tissues leading to recurrence and severe complications. With the help of the radiophysicists in improving distribution of the needles and perhaps with improvement in roentgen-ray-radiation technique, even better results are awaited in the future.

Waterman, G. W., and Raphael, S. I.: The role of interstitial radium therapy in the treatment of cancer of the cervix uteri. Am. J. Roentgenol. 68: 58-62, July, 1952.

Breast Lesions—Early Diagnosis

The most reliable diagnostic procedure in any lesion of the breast is biopsy and, in cases in which the surgeon performs a biopsy, it is always better to remove the entire lesion for examination. Other means of diagnosing breast lesions available to the general practitioner in his office are transillumination of the breast lesion, needle biopsy, aspiration of fluid from a cyst, and cytological examination of secreted or expressed discharge from the nipple. Cancerous lesions cannot be diagnosed by transillumination. Pathologists in general hesitate to recommend needle biopsy of breast lesions. Surgical biopsy is easily done and the correctness of the diagnosis in routine cases when made by experts is almost 100 per cent. Cytological examination may be applied to the diagnosis of breast lesions by means of examinations of secretions from the nipple. This is a method that can easily be used in office

up with Cancer



practice. Cytological examination of the nipple discharge not only may lead to early diagnosis of certain carcinomas of the breast, but it is often helpful in diagnosis of mazoplasia, so-called chronic cystic mastitis, and papilloma. It is the only method short of a partial mastectomy by which carcinoma can be diagnosed or ruled out in cases of bleeding from the nipple, if no tumor is palpable. The possibility is discussed of expressing a nipple secretion in a large percentage of women who have no complaints of breast lesion and no nipple discharge for the purpose of detecting papillomas and carcinomas before they produce a spontaneous nipple discharge. Roentgenography has failed to be of value in the diagnosis of breast lesions, but two authorities in the field of breast cancer were able to diagnose mazoplasia, chronic cystic mastitis, and papilloma.

Saphir, O.: Early diagnosis of breast lesions. J. A. M. A. 150: 859-861, Nov. 1, 1952.

Radioactive Colloidal Gold in Cancer Therapy

Radioactive colloidal gold (Au^{198}) has a half-life of 2.7 days, which is long enough to be practical and short enough to avoid long-continued irradiation of the patient. It can be administered by several routes, each producing a different end result. Au^{198} has found its greatest success and widest application in the management of selected cases of recurrent pleural effusion or ascites caused by cancer. A closed remote system suitable for instilling the material into the pleural or

peritoneal cavity was devised to simplify handling, to minimize exposure of personnel to radiation, and to reduce the possibility of spillage and radioactive contamination.

Rose, R. G.; Osborne, M. P., and Stevens, W. B.: The intracavitary administration of radioactive colloidal gold. New England J. Med. 247: 663-667, Oct. 30, 1952.

Pathogenesis of Cancer

All indications point to disordered function of the endocrine system as the principal cause of the origin and continued growth of cancer. It has been found that chemical function does change, as established in studies already made of that function in various decades of life. Certain types of cancer tend to occur at a time of life when the manufacture of the steroid hormones of the body tends to change—at puberty and at the menopause.

Studies in the laboratory support the conclusion that there occurs a shifting balance in the body of the chemicals, hormones, produced by the endocrine system. Some of the endocrine chemicals are composed of proteins of unknown molecular types, incapable of being synthesized. Members of another group called "steroids" are of known structure and can be prepared artificially. It has been found that (1) each individual has a remarkably characteristic and constant pattern of steroid-hormone excretion, (2) dietary deficiency, disease, and the ageing process change the individual pattern, and (3) abnormalities of excretion patterns are present if the patient has cancer. Obviously, abnormalities in the kinds

and amount of steroid hormones excreted by cancer patients could be either the cause or the result of the cancer. In order to determine whether the abnormal steroid production was the cause and not the result of the cancer, it was necessary to study the urine of patients who would acquire cancer in the future, for example, individuals with definitely precancerous diseases (xeroderma pigmentosa and Paget's disease of bone). Substantial progress has been made in correlating the compounds originally formed by the endocrine glands with their modified products excreted in the urine. The procedure adopted was to incorporate tracer atoms, either heavy or radioactive, in the molecules of the compounds naturally formed. The most important contribution of the Strang Cancer Prevention Clinic, made possible by the examination of some 40,000 individuals, has been to establish knowledge of the appearance and expected course of precancerous changes of tissue. This study has provided groups of individuals with characteristically precancerous changes that can safely be submitted to detailed studies in an attempt to ascertain the exact error of body chemistry leading to the development of the changes, that, if uncorrected, would convert them into fully developed cancer. On the basis of knowledge of hormone manufacture in man, it is hoped to correct the abnormality when defined, before cancer has fully developed and when the abnormal tissue still can return to normal stages under treatment.

Rhoads, C. P.: Fundamental concepts relating to pathogenesis of cancer. New York State J. Med. 52: 1640-1644, July 1, 1952.

Radiation Therapy— Injurious Effects

The clinical occurrence of untoward radiation sequelae in the radiation therapy of carcinoma of the uterine cervix is analyzed. Complications are divided geographically into three main types: (1) reactions in the bowel, (2)

those referable to the genitourinary system, and (3) those occurring locally in the uterus and parametria. They are further divided according to severity. Success in treatment has been found to depend upon the stage of disease and the dose delivered in relation to the treatment time. Should untoward reactions be accepted as a necessary sequel to successful treatment? In the case of advanced lesions the answer is in the affirmative and, in the case of early ones, it is negative. The findings suggest that some complications may be decreased by improvements in treatment techniques, which will allow for more adequate distribution of radiation to the lateral extensions of the tumor without intensifying the dose to the paracervical regions.

Nolan, J. F., and Du Sault, L.: The elimination of untoward radiation sequelae in the treatment of carcinoma of the uterine cervix. Surg., Gynec. & Obst. 94: 539-542, May, 1952.

Treatment of Cancer

Surgery and irradiation still remain the mainstays of treatment for most types of cancer. While anticancer drugs and sex hormones prolong life and make it more comfortable for the cancer patient, they are for the most part palliative rather than curative. Many cases of cancer with extensive local spread have been relieved of distressing symptoms through the use of the more radical surgery now made possible by advances in anesthesiology, blood and electrolyte replacement, endocrine substitution, and control of infections. Surgical removal of metastatic lesions in distant organs has in general not proved effective, although there are exceptions. Many palliative operations have been developed, including new and improved techniques for the relief of malignant obstructions of the urinary, gastrointestinal, and biliary tracts, and operations designed to inhibit tumor growth by alteration of the hormone balance (castration and adrenalectomy).

Many advances in radiation therapy of cancer are by-products of research

on atomic energy. The radiotherapist now has at his command supervoltage roentgen-ray generators, new types of radiation from the cyclotron, betatron, and other particle accelerators, in addition to medium voltage roentgen rays, radium, and radon. It is unfortunate that clinical results have not been greatly improved by the application of these new techniques. The use of radioactive isotopes often permits better localization of radiation than has heretofore been possible.

Only a few of the anticancer drugs tested have had wide clinical trial. Nitrogen mustards produce temporary remissions in a high percentage of patients with Hodgkin's disease, lymphatic leukemia, lymphosarcoma, giant follicular lymphoblastoma, and mycosis fungoides when administered intravenously. Results with triethylenemelamine have been similar to those obtained with nitrogen mustard in the lymphomas. Folic acid antagonists and urethane have a limited field of usefulness. Certain kinds of cancer have benefited from hormone therapy. Estrogens have been used to good advantage in cancer of the prostate, postmenopausal carcinoma of the breast, carcinoma of the bladder and chorioepithelioma. Androgens exert a palliative effect in carcinoma of the breast with extensive metastasis.

In addition to specific therapy for cancer, it is important that the patient's morale be maintained. The relief of secondary infection with antibiotics; of disturbances in fluid, electrolyte, and nutritional balance with parenteral fluids; of any associated congestive heart failure with standard remedies; and of anemia with transfusions will often do more to make the patient comfortable than any specific measures available.

Basic research seems to be as important as "project" or restricted research in seeking a solution to the problem of specific anticancer therapy. Warning is given against overoptimism concerning new, inadequately tested

remedies. Enthusiastic publicity concerning new "wonder drugs" can result in incalculable harm to the health of the public.

Anon.: Treatment of cancer. [Editorial.] J. A. M. A. 149: 1400-1402, Aug. 9, 1952.

TEM Therapy

Fifteen patients with Hodgkin's disease, chronic lymphatic leukemia, and multiple myeloma were given oral doses of from 10 to 20 mg. of triethylenemelamine (TEM) over an eight-to-ten-day period. Therapy was continued in some cases after an interval of two or three weeks with smaller doses of 2.5 to 5.0 mg. weekly for varying periods of time. There were very few immediate gastrointestinal side effects from the drug. The immediate palliative effect in 50 per cent of the patients with Hodgkin's disease was good. Itching, cough, and pains were either relieved or disappeared. Enlarged peripheral lymph nodes were diminished and fever subsided. Unfortunately the remissions obtained were of short duration. No improvement was noted in five of a group of six patients with chronic lymphatic leukemia, lymphosarcoma, or carcinoma of the breast with metastases. TEM produced a severe depression of the granulocyte and platelet formation in 40 per cent of the cases. One case of fatal aplastic anemia developed. This effect on the bone marrow appeared two to three weeks following commencement of the therapy and persisted for three to four months. Intensive treatment with blood transfusions, B₁₂, folic acid, and antibiotics had little effect on this manifestation.

Hansen, P. B., and Bichel J.: Triethylene melamine therapy in Hodgkin's and other malignant diseases. Acta Radiol. 36: 469-476, Dec., 1951.

Gastric Cancer

Patient delay is prominent in those with mild gastric symptoms, any of whom may have gastric cancer, and has its origin in ignorance, fear, and the hope that the symptoms will get better by themselves. Reduction of delay on

the part of the patient is the most obvious single factor that can lead to earlier diagnosis and treatment of gastric cancer. Second only to patient delay is the delay that occurs after the patient sees a physician. Often months are lost between the first visit to the physician and a definitive diagnosis. The clinician urgently needs simpler and more reliable diagnostic aids at lower cost.

It is emphasized that gastric cancer is a curable disease. Cure rates compare favorably with those of cancer of other organs generally considered curable. Three-year cures in gastric cancer have increased nearly threefold in the past ten years. More patients are salvaged than ever before. The present study is based on a series of 687 cases of gastric cancer admitted to the New York Hospital between 1932 and 1951. In these cases delay on the part of the patient averaged about eight months. Operability has increased in the past ten years from 15.5 per cent to 33.8 per cent. This evidence of progress may be due to more radical surgery or to earlier diagnosis. Each year since 1940 more extensive operations have been performed, some of them palliative. Palliative resections have little to do with the cure of the cancer but they are a contribution to patient comfort and have a real place in treatment. Operative mortality has decreased steadily in the past decade. Many factors are responsible for this, the most important being the chemotherapeutic and antibiotic agents. The increase in three-year cures in gastric cancer is ample justification for the increased scope of surgery in the past ten years.

While analysis of the series of cases clearly shows the advantages of the more radical surgery performed during the past decade, one fundamental question still remains unanswered: Is gastric cancer being diagnosed and treated earlier? The roentgenographic method, with all its limitations, is the best diagnostic aid generally available. A plea is made for the intelligent

evaluation of this method in every patient suspected of having gastric cancer. Early results in cytological examination of gastric contents, using the balloon technique for obtaining specimens, suggest another approach to the diagnosis of gastric cancer that is at least as accurate as roentgenography. The cytological method has an inherent accuracy that roentgen-ray diagnosis lacks in that it reveals the basic pathological nature of the growth. Since about 75 per cent of patients with gastric cancer have a low free acid level or no free acid, this finding is a valuable diagnostic aid. A new method, utilizing a cation exchange resin, will soon be available to clinicians that will enable the physician to determine in his office the presence of free gastric acid in the urine without the unpleasantness of gastric intubation. Stool examination for occult blood if practiced more extensively would doubtless lead to earlier diagnosis of gastric cancer. Gastroscopy is a helpful diagnostic aid but does not approach the roentgenogram in over-all accuracy.

Cooper, W. A.: Patients, physicians, and gastric cancer. J. A. M. A. 150: 688-692, Oct. 18, 1952.

Roentgen-Ray Therapy in Carcinoma of the Bronchus

An analysis was made of the effect of roentgen-ray therapy on patients with carcinoma of the bronchus, with at least two years of follow-up on every patient. Of 218 patients, 201 were men and seventeen women, a proportion of 12 to 1. Before deciding for or against radiotherapy for a patient with inoperable bronchial carcinoma two questions must be answered: (1) Is there any distressing symptom that requires immediate palliation? and (2) If there are no distressing symptoms, can the patient withstand a course of treatment planned to deliver a dose of 4000 to 5000 r to the tumor? Roentgen-ray therapy affords considerable alleviation to mediastinal obstruction and almost constantly stops distressing hemop-

tysis. Supervoltage roentgen-ray therapy appears to be preferable in patients with mediastinal obstruction. A high dosage is more likely to be obtained using supervoltage roentgen rays. The patient will be more likely to derive some benefit if the cancer is in the upper lobe and symptoms have been present for more than six months. About half the patients given roentgen-ray therapy improved symptomatically after treatment. Less than one fifth lived longer than a year. Age had no effect on the course of the disease. Anaplastic lesions had the greatest chance of immediate benefit but slightly worse prognosis. The immediate and final outlook was slightly more favorable in patients where the cancer was situated in an upper lobe bronchus. Survival rate was definitely improved when doses of over 4000 r were given.

Brown, D. E. M.: X-ray therapy and carcinoma of the bronchus; an analysis of the effect on 218 patients of irradiation of the primary lesion. Brit. J. Radiol. 25:472-475, Sept., 1952.

Roentgen-ray Therapy of Uterine Cancer

The greatest present possibility of improving results particularly in the treatment of the advanced cases of carcinoma of the cervix lies in the understanding of the role and in the adequate utilization of external pelvic roentgen-ray radiation. No other form of treatment applied to any other major form of cancer can boast of as high a percentage of permanent results as that which has been obtained by the adequate association of external pelvic roentgen-ray therapy and intracavitary radium treatment of cervical carcinoma. Successful treatment of advanced carcinoma of the cervix by combined radium and roentgen-ray therapy depends on devoted effort and careful evaluation of the clinical, pathological, physical, and radiobiological facts involved. Best results are achieved when radiotherapy of cervical carcinoma is considered primarily from the point of view of external roentgen-ray radiation

and when internal radium treatment is thought of merely as an adjunct intended to compensate for the inherent deficiencies of the external irradiation. Irradiation of all parts of the tumor as frequently and as evenly as possible should be the guiding principle. Treatment should be protracted, preferably over at least eight weeks in order to eliminate the complication of irradiation sickness. Cervical carcinoma being highly radiosensitive and radiocurable requires only a moderate daily dosage. Under favorable circumstances (thin patients) external roentgen-ray radiation alone has controlled rather advanced cases of cervical carcinoma. In general, however, external roentgen-ray radiation needs to be complemented by internal radium treatment. The use of transvaginal roentgen-ray therapy instead of radium has as its main advantage the possibility of more extensive utilization of external roentgen-ray radiation.

Regato, J. A. del: The role of roentgen therapy in the treatment of cancer of the cervix uteri. Am. J. Roentgenol. 68: 63-65; disc. 65-71, July, 1952.

Treatment of Oral Cancer

Oral cancer is predominantly a male disease, occurring ten times more often in men than in women. Ninety-eight per cent of the lip cancers and 80 per cent of the other intra-oral lesions occurred in males. The average age of the patients was about 63 years. Oral cancer tends to be a local disease and remote metastases are exceptional.

The term "oral cancer" includes cancerous lesions of the lip and oral cavity, back to and including the anterior pillars of the tonsils and the base of the tongue. In patients who were suffering from syphilis (about 3 per cent of the cases) the cancer was more resistant to treatment and prognosis was relatively poor. Eight per cent of the tongue lesions were associated with syphilis. Leukoplakia is unquestionably precancerous or may become cancerous at any time. Ulceration, bleeding, or irregularity of the surface should

suggest cancerous change in leukoplakia. Cancer of the buccal mucosa has been found to occur in those who habitually chew tobacco. A few cases have been associated with foreign-body irritation.

The combined efforts of surgeon, radiologist, dental consultant, and neurosurgeon are enlisted in the treatment of oral cancer in the Toronto General Hospital. Diagnosis is confirmed by biopsy and a plan of treatment agreed upon. Early diagnosis is very important and directly determines prognosis. Treatment of oral cancer by the combination of radiotherapeutic measures and surgery has proved to be satisfactory and the results achieved are gratifying.

If radiation therapy is to be successful, it is necessary to obtain a tumorlethal dose that will cause the least possible damage to the surrounding tissues. It should be carried out only in centers staffed by highly trained and experienced personnel. The response of the primary lesion to radiation depends not so much on the histological type of cancer as on the location of the lesion and its accessibility to radiotherapeutic measures.

In treating cervical metastases surgically, a block dissection of the affected side of the neck should be done with removal of the submaxillary salivary gland, sternomastoid muscle, and jugular vein. Involvement of lymph nodes on both sides of the neck does not necessarily mean that the case is hopeless. Radiological treatment as a palliative measure in advanced cases usually results in temporary regression and often controls the disease. The high incidence of lymphatic spread of tongue and intra-oral lesions justifies prophylactic dissection, particularly in the younger age group. More than 150 patients with oral cancer who have lived five years had undergone extensive block resections of the neck or excision of the jaw. The material presented here includes 1128 cancers of the lip, 342 cancers of the tongue, and 497 lesions

of other sites in the oral cavity during the period 1929 to 1945.

Wookey, H.; Ash, C.; Welsh, W. K., and Mustard, R. A.: *The treatment of oral cancer by a combination of radiotherapy and surgery*. *Ann. Surg.* 134: 529-538; disc. 538-540, Oct., 1951.

Estrogens in Prostatic Carcinoma

A study was made of the effect of various estrogenic preparations on the reticulo-endothelial organs and on the prostate and uterine horns of 167 guinea pigs, which were divided into groups of intact males and orchiectomized and ovariectomized animals. The estrogens used were estradiol benzoate, estrone, stilbestrol, stilbestrol dipropionate, D.B.E. (α , α -di(*p*-ethoxyphenyl)- β -phenylbromoethylene), and dienestrol.

The estrogens were found to stimulate the reticulo-endothelial macrophages in the spleen, liver, and lymph nodes. Prolonged estrogen treatment or stimulation by large doses of estrogen led to mobilization of the macrophages in these organs and to their accumulation in the secondary sex organs, such as the prostate or uterine horns. Orchiectomy also stimulated the macrophages. The combination of orchiectomy and estrogenic treatment accelerated the stimulation and mobilization of the cells. It is believed that the macrophages in the prostate may be formed partly *in situ* but more likely come from the spleen and other reticulo-endothelial organs as a result of estrogenic stimulation. Prolonged treatment with estrogens, particularly in orchiectomized animals, produced marked fibrosis in the prostate. This is probably the result of transformation of the macrophages into fibroblasts and later into fibrous tissue. It is suggested that this is the manner in which the beneficial sclerosis occurs in prostatic carcinoma after endocrine therapy. Stimulation of the reticulo-endothelial system probably increases the general defense of the body against cancer.

Nicol, T.; Helmy, I. D., and Abou-Zikry, A.: *A histological explanation for the beneficial action of endocrine therapy in carcinoma of the prostate*. *Brit. J. Surg.* 40: 166-172, Sept., 1952.



a glance . . .

one-minute abstracts
of the current literature
on cancer . . .

Gleanings from the Scientific Session of the Annual Meeting American Cancer Society, Inc., October 21-22, 1952

Irradiation in Breast Cancer

The problem of treating mammary cancer is complicated by spreading of the tumor through the internal mammary chain. At least 5000 r must be delivered to the chain. The usual procedure is to treat the cases of mammary cancer by surgery first and to irradiate them afterward. It has been a diagnostic procedure to find out what is happening in the internal mammary chain before deciding on treatment. It is extraordinary how methods will work in the hands of enthusiasts and not in the hands of other people. Of 125 cases, all nodes were free in forty patients, the axillary nodes only were invaded in forty-two patients and forty-three patients had invasion of their internal mammary nodes.

Handley, R. S.: The role of irradiation in the management of breast cancer. Discussion.

Rotational Therapy in Cancer

Rotational therapy offers an ideal approach in many locations of the body, especially when treating tumors of the pituitary fossa, the larynx,

esophagus, bladder, corpus uteri, and uterine cervix. Lesions of the lung and upper abdomen are best treated by cross firing. If irradiation is to be successful, the entire tumor and its surrounding lymphatics must receive a cancerocidal dose of irradiation. After treating nearly five hundred cases at the Lahey Clinic, Hare is convinced that it is a means of delivering radiation with less damage to the normal surrounding tissue, a more accurate means of delivering this radiation, and one that avoids the hot spots so common from the cross-fire technique.

Hare, H. F.: Preliminary results in the use of rotation therapy. Discussion.

High-Energy Electron Accelerators in Therapy of Cancer

The first patient to receive electron-beam therapy had an adenocanthoma with involvement of facial nerve and bone. There was no evidence of the cancer more than a year later. More recently he had developed nodes in the lower neck beneath the field of irradiation. The electron beam has also been

used for primary cancer of the breast, of the tonsil and hypopharyngeal lesions. There is important research still to be done along the lines of the relative sensitivity ratio of normal to cancer tissues in humans.

Harvey, R. A.: The place of high-energy electron accelerators in the treatment of cancer.

Abnormal Lung Shadows—

Diagnosis

Carcinoma of the lung is the most detectable of any internal cancer during its silent and localized stage. It should also be the most curable. Millions of people have their chests screened every year by the Tuberculosis Society and those having abnormal shadows are directed through the tuberculosis hospitals with considerable delay in many cases. A small lesion not more than the size of a lima bean may include the segmental bronchus and be magnified by resulting segmental atelectasis. It is these shadows that cause so much confusion and delay in the asymptomatic patient. These shadows may be twenty-five times the size of the shadow of the lesion itself. These are the patients that may be directed to the tuberculosis hospitals. Negative bronchoscopic and cytological tests do not rule out cancer.

Overholt, R. H.: Confusion in the diagnosis of abnormal lung shadows. Discussion.

Survey methods and conventional methods leave much to be desired in early diagnosis of cancerous pulmonary lesions. Postmortem examinations of the chest and lungs compared with pre-mortem examinations show that many pulmonary lesions are not recorded by conventional methods.

Pendergrass, E. P.: Confusion in the diagnosis of abnormal lung shadows. Discussion.

The great problem of differential diagnosis is illustrated by cases of hernia of the omentum, accumulation of fat in the chest, unilateral Hodgkin's disease, neurofibrosarcoma, a huge anterior meningocele, metastasis from a

Wilms's tumor, pulmonary tuberculosis, adenocarcinoma, etc. Radiology has accomplished a great service in being able to point out in a particular patient an abnormality that deserves serious consideration. Chest lesions are extremely difficult to see on casual examination.

Hodges, F. J.: Confusion in the diagnosis of abnormal lung shadows. Discussion.

Accurate diagnosis will depend on extremely close cooperation between the clinician and the radiologist. The patient with a questionable lesion should have bronchoscopy and biopsy immediately. A relatively high kv. technique gives the most information and has helped in the more prompt diagnosis of early carcinoma.

Robbins, L. L.: Confusion in the diagnosis of abnormal lung shadows.

Curative and Palliative Radiation Therapy

It is important that the treatment of cancerous tumors be centralized to special well-equipped radiation institutes. Radiotherapy requires long personal experience, meticulous follow-up of treated patients, and a great knowledge of physical and biologic principles of radiotherapy. Palliative radiotherapy only has been administered in 8.8 per cent of 3376 cases of cervical carcinoma treated at Radiumhemmet, Stockholm, with remarkably good results in more than 50 per cent of the cases.

Kottmeier, H. L.: Indications for curative or palliative radiation therapy. Discussion.

Radiation Therapy—Complications

There is no reason why a patient should not be made comfortable during the time he receives treatment by giving him something to take care of radiation sickness. The late effects of radiation are due to the biological reaction of early therapy. The reaction has nothing to do with voltage. I have not seen a case of carcinoma develop-

ing in the severe skin reactions from intensive, single four- to six-weeks courses of radiation.

Stone, R. S.: *Complications following radiation therapy. Discussion.*

Irradiation in Breast Cancer

The preoperative procedure consists of high doses of roentgen rays. One hundred fifty-one cases of stages II, III, and IV breast cancer were treated by irradiation from 1936 to 1946, with forty-four cases apparently symptom-free and fifty-seven living after five years. There were sixty-nine late metastases out of 151 cases. There were post-irradiation complications in sixty-two cases. Treatment of breast cancer by roentgen-ray therapy alone is only in its experimental stage and cannot be regarded as routine treatment. It is too dangerous.

Baclesse, F.: *The role of irradiation in the management of breast cancer.*

Rotation Therapy of Cancer

Dose distribution in rotation therapy is favorably influenced by the penetrating power of the ray. So far cancer of the esophagus has been the chief target for rotational therapy. Of 242 cases treated by rotation therapy, six are living more than five years. In all six cases the histological diagnosis was squamous-cell carcinoma. Patients with adenocarcinoma of the esophagus and cardia and carcinoma of the gastric fundus did not in any case benefit from rotation therapy longer than fifteen months. Rotation therapy in this region is still mostly palliative. Many patients were able to swallow until the very end and death was due to metastases.

Nielsen, J.: *Preliminary results in the use of rotation therapy.*

Surgery in Uterine Cancer

Often an early case of stage-I carcinoma of the cervix did not respond to radiation therapy. Surgery is being done in carcinoma of the cervix because of radiation resistance and radiation sensitivity. The only criterion for

surgery is whether the surgeon himself thinks he can do good surgery and come out with a live patient. Of 100 patients with truly invasive carcinoma of the cervix, stages I and II, seventy-five are alive and well at five years following operation. Of the stage I, 18 per cent had positive nodes and 41 per cent of those are alive and well at five years. Of the stage II, 32 per cent had positive nodes and only nine of those patients are alive and well at five years. The extent of the disease has a lot to do with the curability of cancer of the cervix. Eventually we will be able to give a test dose of radiation to patients with cervical carcinoma and decide whether or not we should use radiation or surgery. Considerable experience is required before a surgeon attains a certain standard of excellence in learning to perform the radical operation for cancer of the cervix.

Meigs, J. V.: *Round Table—End results in the treatment of uterine cancer.*

Radium and Radioactive Isotopes in Therapy

The ideal type of radiotherapy would be the uptake by tumor cells of an ionizing agent, the action of which would be limited to these cells. Beta emitters such as iodine¹³¹, P³², and Au¹⁹⁸ almost achieve this ideal. A tumor selectively absorbing these beta emitters can be heavily irradiated without appreciable damage to the surrounding structures. Certain types of thyroid tumors, leukemia, or reticulo-epithelial tumors have responded to therapy with the beta emitters, the disadvantage of the therapy being either spottiness of uptake or too diffuse irradiation of sensitive structures such as bone marrow.

Radiation techniques have evolved in order to give homogeneous distribution of the dose, avoiding "cold and hot spots," while controlling the spread beyond the area thought to contain the tumor. One of the few well-proved facts in radiotherapy is that in the use

of interstitial, intracavitary, or surface applicators, continuous low-intensity gamma-ray irradiation delivered over five or ten days yields the best results with minimum dosage. The development of dosimetric systems showed vividly the necessity of accurately determining the volume to be treated and when to use definite geometrical patterns. A failure is bound to come if the minimum amount of radiation does not reach all extensions of the tumor. It was found that treatment by intracavitary or interstitial radium was only occasionally successful in lesions in the tonsillar area, base of tongue, soft palate, and lateral pharyngeal wall.

Through the radiotherapeutic team of physicist and radiotherapist, combining clinical experience with the necessary knowledge of physics, gamma-ray therapy is performed in a way comparable to the most elaborate radical surgery. In gamma-ray therapy the radiotherapeutic team finds a field for development for the almost infinite variety of strength, shape, and physical characteristics of gamma emitters. If done rashly and without enough caution, the replacement of radium needles and tubes by equivalent sources of cobalt⁶⁰ could be detrimental. Cobalt, tantalum, sodium, bromine, selenium, gold, cesium, and europium are being used in gamma-ray therapy. There is no advantage whatsoever in replacing radium needles or tubes in the treatment of the majority of lesions that can be treated by patterns of the Paterson-Parker system. Radon seeds have proved of real value in some very defi-

nite types of lesions in certain locations. The use of beta-ray emitters is justified for benign conditions of the eye and an occasional early squamous-cell carcinoma of the conjunctiva. Aside from early tiny lesions the use of beta-ray transmitters would possibly result in diminished cure rates in skin carcinomas. So far, expectations with interstitial injection of beta-ray emitters in solution have met with only a small degree of clinical success.

Fletcher, G. H.: Newer concepts in the use of radium and radio-active isotopes in the treatment of cancer.

Cobalt-Beam Therapy in Cancer

This year interest has concentrated upon cobalt-beam therapy. After about one year's operation it is concluded that effectiveness of radiotherapy will be increased greatly by the routine use of this form of irradiation postoperatively in gastric and rectal cancer. A continued determined effort is being made to establish a cure rate in early deep-seated lesions such as those of the lungs, esophagus, and rectum. The field of palliation is extending to include the ofttime neglected sites such as the bulky confines of the stomach, moderately advanced esophageal and rectal carcinoma, and a limited number of rare, deep-seated lesions. Cobalt therapy is also being used legitimately in a large group of conditions now being reasonably well handled by conventional methods, such as laryngeal, intraoral, and cervical carcinoma.

Smith, I. H.: Newer concepts in the use of radium and radioactive isotopes in the treatment of cancer. Discussion.

How can a physician say that a disease is incurable when death is not present; those only are incurable in which death is present. . . .
Paracelsus (1493-1541).

Early Detection of Carcinoma of the Stomach

Ross Golden, M.D.

Early detection of cancer of the stomach may mean detection of a small cancer, or of cancer before it has spread beyond the walls of the stomach, or of cancer before it has produced symptoms. Small cancers may already have metastasized before the disease is recognized and removed.

Two direct objective methods of detection of cancer of the stomach are roentgenography and gastroscopy. It is unfortunate that these two methods are often regarded as rivals rather than as complementary methods, each of which has its particular advantages and limitations.

Carcinoma of the stomach can be detected by roentgen-ray methods only when it has produced a recognizable modification of the form or of the movements of the stomach. First the abnormality must be demonstrated and then it must be recognized as the result of cancer. This depends upon two factors: (1) the location of the growth in the stomach, and (2) the gross growth characteristics, not the microscopic appearance of the cells, of the neoplasm.

Location of the Growth in the Stomach

A study of the roentgenograms of 315 proved cases of carcinoma of the stomach seen at the Presbyterian Hospital in New York showed that approximately 75 per cent arose in the antrum, 20 per cent in the body or media, and 5 per cent in the fundus. The fundus may be defined as that portion of the stomach lying roughly above the level of the cardiac orifice, the body or media as that portion between the cardiac orifice and the incisura angularis, and the antrum as the portion that turns to the right and extends to the pylorus.

Dr. A. Purdy Stout made a similar

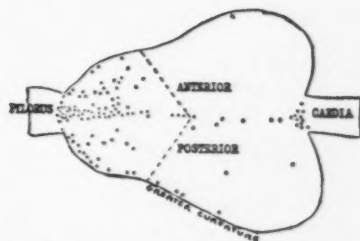


Figure 1. The location of 120 carcinomas in 120 resected stomachs (Stout's diagram).

study of 120 resected cancers of the stomach. His diagram is reproduced in Fig. 1. It is obvious that the distribution of these cancers is similar to that described in the preceding paragraph.

It is apparent from these two studies that the great majority of carcinomas arise in the lower half of the stomach. This is the motor portion, accessible to palpation and pressure under the fluoroscope, where abnormalities of form and disorders of movement can be most easily demonstrated. Carcinomas of the fundus in general are much more difficult to detect; and they present technical problems beyond the scope of this discussion.

Gross Growth Characteristics

Carcinoma of the stomach arises in the mucous membrane but grows in different ways in different individuals. Classification of these growths according to the microscopic appearance of the cells is useless from the standpoint of understanding the effect of the neoplasm on the stomach wall. Further-

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Figures 1, 2, 6A, and 7 are reproduced from Golden: Diagnostic Roentgenology, Volume 1, The Williams and Wilkins Company, Baltimore.



Figure 2. The fungating type of carcinoma of the stomach. A, A large filling defect is shown on the greater curvature of the antrum.

more, the characteristics of the cells may vary in different parts of the growth. On the other hand the manner in which the growth involves the wall is of great importance. The gross growth characteristics form the basis of Stout's classification of carcinoma of the stomach (Golden and Stout):

(1) fungating; (2) penetrating; (3) spreading—(a) superficial type, (b) linitis plastica type; (4) advanced, unclassifiable.

FUNGATING growths were present in 26 per cent of 342 cases seen in the Department of Surgical Pathology at the Presbyterian Hospital between 1937 and 1949. This type forms a mass projecting into the lumen. It may reach a large size before it penetrates into the submucosa, and it metastasizes late. It may or may not ulcerate. Because of its mass the fungating growth is relatively easy to detect (Fig. 2).

The PENETRATING type apparently extends through all layers of the stomach wall to the serosa early in its development. It destroys and replaces the muscle. It invariably ulcerates. This type was found in 32 per cent of the 342 cases. Because of the ulceration, the lesion is easy to detect but it may be difficult to differentiate the excavation in the penetrating carcinoma from some of the benign peptic ulcers. This aspect of the problem cannot be discussed here (Fig. 3).

The SUPERFICIAL SPREADING type extends along the wall in the mucosa and submucosa and in some cases is limited to the mucous membrane. It may produce tiny nodular elevations on the surface (Fig. 4). It may ulcerate. This is the type of carcinoma found in the mucous membrane adjacent to the margin of some gastric craters that have the structural characteristics of benign peptic ulcers. The new growth may completely encircle the crater but usually involves only a portion of its circumference. The carcinoma adjacent to the benign crater may itself ulcerate producing a double or a lobulated crater shadow (Fig. 5). In its later stages the malignant cells pass to the serosa through the muscularis without destroying or replacing the muscle cells. In one instance (Fig. 6) the mucosa of the entire stomach was replaced by carcinoma, with malignant



Figure 2. B, The photograph of the specimen shows a mass projecting from the mucosa into the lumen of the stomach.



Figure 3. The penetrating type of carcinoma of the stomach. A, The roentgenogram discloses evidence of a large flat ulcer on the lesser curvature.

cells lying among the muscle bundles of the hypertrophied muscularis; this stomach expelled barium rapidly but the contractions were unlike flexible peristaltic waves. In other instances a slight stiffening or flattening of the wall was present at the site of involvement of a relatively small area with no extension into the muscularis itself. The reason for this phenomenon is not clear.

SUPERFICIAL SPREADING carcinoma comprised 11 per cent of the 342 cases, of which approximately four fifths were associated with ulceration, either with a peptic ulcer or with an excavation in the cancer itself. The abnormality is more easily detected if an excavation in the carcinoma is present. As a result of follow-up observations on some of the early cases, Stout believes the prognosis is better in this type of cancer than the average of all cancers of the stomach.

The LINITIS PLASTICA type of spreading carcinoma extends along the wall in the submucosa, the muscle coat, and the subserosa. It does not destroy the mucosa until very late in the disease (Fig. 7). It is often associated with



Figure 3. B, A low-power photomicrograph of the margin of the crater shows normal muscle cells on the left. On the right, adjacent to the crater, the muscle is replaced by carcinoma.



Figure 4. The superficial spreading type of cancer of the stomach. A, The roentgen-ray examination discloses marked antral spasm, interpreted as antral gastritis. Gastroscoy disclosed small carcinomatous nodules on the anterior wall of the antrum where about ten months previously an area of atrophic mucosa with superficial erosions had been seen.

high stiff mucosal folds, closely resembling those associated with gastritis—in some cases both on roentgen-ray and gastroscopic examination (Fig. 8). In most cases the malignant cells stimulate the growth of fibrous tissue, which may vary from very slight to extreme. The linitis plastica type of carcinoma was found in 6 per cent of the 342 cases.

Stout concludes his classification

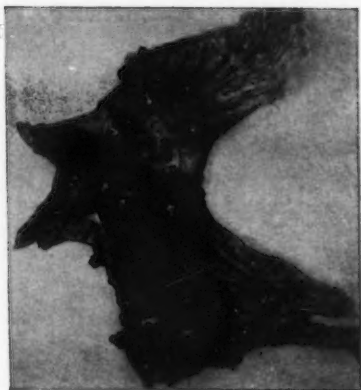


Figure 4. B, The resected specimen showed an area of carcinomatous infiltration about 6x9 cm. along the lesser curvature and extending on to both anterior and posterior walls, outlined by arrows. (The pylorus is on the left; the lesser curvature, on the right.) In its center were small nodules about 3 to 5 mm. in diameter with slightly depressed areas of ulceration. The involved area of mucosa was immovable over the muscle. Microscopic examination showed that the carcinoma involved only the mucosa and had not extended into the submucosa.

with the group of carcinomas that are too far advanced to be classified with certainty under these headings. This group comprised 25 per cent of 342 cases.

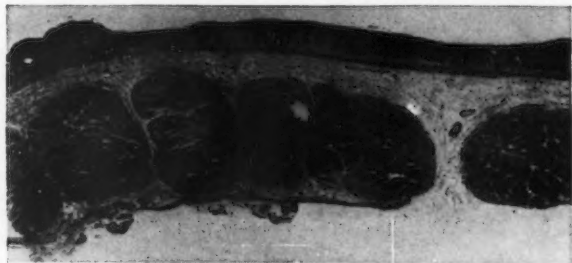


Figure 4. C, A low-power photomicrograph shows carcinomatous nodules on the left with atrophic mucosa on the right.

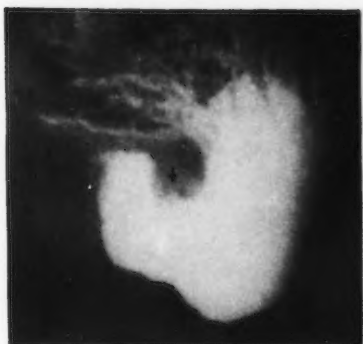


Figure 5. Superficial spreading carcinoma with a peptic ulcer. A. The roentgenogram of the barium-distended stomach discloses a crater shadow on the lesser curvature (arrow). Other projections disclosed a double contour of the apex of the crater.

It is quite obvious that the problem of detection of the carcinoma by roentgen-ray methods is different in these groups.

Growth Characteristics and the Roentgenographic Examination

The fungating carcinoma is the easiest of all to detect by roentgen-ray



Figure 5. B. A supine spot-film with the ulcer en face discloses a trilobed appearance.

methods because of the mass that produces a filling defect in the barium shadow. It may be stimulated by any mass that projects into the lumen from the stomach wall, for example a small leiomyoma, a polyp, or a localized mass of so-called giant mucosal folds. If the fungating carcinoma has ulcerated, it is not likely to be confused with another growth.

The penetrating carcinoma is easily detected because of its excavation. The problem is to differentiate it from a benign gastric ulcer. This growth replaces muscle and stiffens the wall over the involved area.

Superficial spreading carcinoma extending along the wall and replacing the mucosa sometimes produces small nodular elevations on the surface and, at least in many cases, obliterates peristalsis over the involved area in spite of the fact that the muscle has not been destroyed. It often causes a localized segmental spasm of the muscularis manifested by an incisura. Small nodules on the mucosa may also be produced by gastritis.



Figure 5. C. The gross specimen disclosed a deep crater with the usual characteristics of a peptic ulcer base. Around part of its circumference was superficial spreading carcinoma which had ulcerated. This shallow ulceration in the carcinoma produced two of the contours of the crater shadow shown in B. (Lesser curvature on right.)

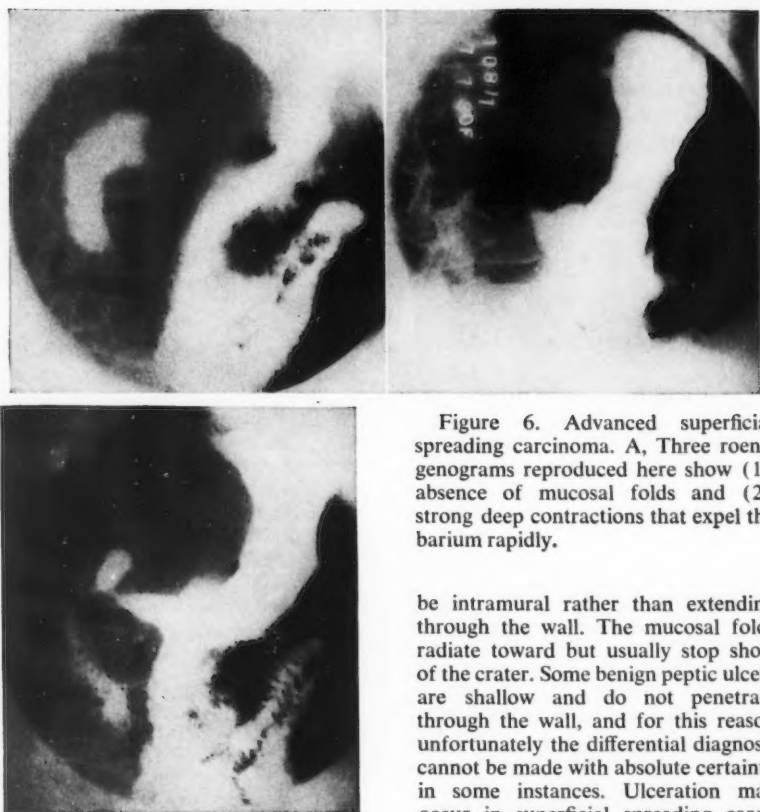


Figure 6. Advanced superficial spreading carcinoma. A, Three roentgenograms reproduced here show (1) absence of mucosal folds and (2) strong deep contractions that expel the barium rapidly.

This is the type of carcinoma sometimes found adjacent to an excavation that has the pathological characteristics of a benign peptic ulcer. The typical benign ulcer extends through all coats of the stomach and has its base on or beyond the serosa. The depth of the benign crater is usually relatively great as compared to its diameter. Its margins are often undermined. The mucosal folds radiating toward it often appear to extend into the crater shadow because the mucosa overhangs the excavation in the muscle.

The excavation in the penetrating or superficial spreading carcinoma is shallow with sloping saucer-like margins, without undermining, and appears to

be intramural rather than extending through the wall. The mucosal folds radiate toward but usually stop short of the crater. Some benign peptic ulcers are shallow and do not penetrate through the wall, and for this reason unfortunately the differential diagnosis cannot be made with absolute certainty in some instances. Ulceration may occur in superficial spreading carcinoma arising in the mucosa adjacent to a benign crater. This may produce a bilobed or trilobed crater.

A differential diagnosis between a penetrating ulcer and an ulcerating superficial spreading carcinoma cannot be made with certainty. Under some circumstances a trial of medical treatment is advisable on the theory that the benign ulcer will reduce in size during a period of two to three weeks. Unfortunately, the excavation in some carcinomas will fill in to a certain extent with carcinoma tissue when the digestive power of the gastric juice is reduced. However, the two types of ulcer respond differently. The benign crater is usually reduced to one half its previ-



Figure 6. B, Photograph of the gross specimen shows thickening of the wall of the stomach from one end to the other. The wall measured 1.5 cm. near the pylorus and 0.5 cm. at the fundus. The mucosa was replaced throughout by carcinoma.

ous size or less in three weeks; it diminishes in transverse diameter as well as in depth. The crater in the carcinoma reduces somewhat in depth but changes very slightly in transverse diameter. Failure of a crater to behave properly



Figure 6. C, A low-power photomicrograph shows the preserved hypertrophied muscle at the bottom of the section. The muscle was hypertrophied and was wider than the entire wall of a normal stomach. The mass of tissue above the muscle was carcinoma which had replaced the mucosa and filled the submucosa. Malignant cells had infiltrated through the muscle bundles to the serosa.



Figure 7. Linitis plastica type of carcinoma. A, The roentgenogram shows evidence of stiffening of the middle third of the stomach with large mucosal folds along the greater curvature. Normal peristaltic waves were seen in the lower part of the antrum.

under treatment can be taken as evidence in favor of malignant disease.

The linitis plastica type of carcinoma is the most subtle, difficult, and dangerous of all. Because it infiltrates to and along the subserosa, it metastasizes relatively early through the lymphatics and spreads over the peritoneum. Because the muscle is not destroyed, the wall is not stiffened until very late and, even when the growth is extensive, apparently normal peristaltic waves pass along the stomach wall. In some cases the mucosal folds may be obliterated but more frequently they are elevated in a manner simulating the effect of gastritis polyposa. In such cases gastroscopy discloses large folds of apparently intact mucosa.

The amount of fibrous tissue associated with the linitis plastica tumor cells in the wall varies greatly in different individuals. In one case prac-

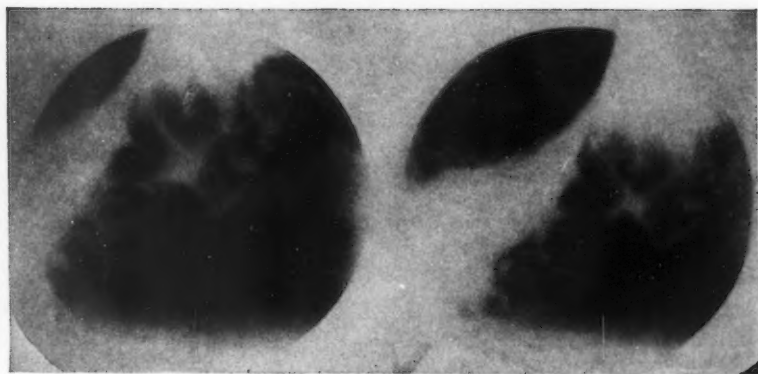


Figure 7. B, Pressure films along the greater curvature show star-shaped shadows produced by barium caught between thickened mucosal folds which resemble crater shadows.

tically no fibrosis was present but the tumor cells spread through the wall in typical linitis-plastica fashion. In well-advanced cases the mucosal folds are large and stiff, and pressure films may show the creases between the folds radiating from a point that resembles a crater shadow but that is not an ulcer.



Figure 7. C, The resected stomach was opened along the greater curvature where thick mucosal folds can be seen. The carcinoma had infiltrated under the mucosa without destroying it and was responsible for the thickened folds. The malignant cells infiltrated to the serosa without destroying the muscle and had produced a moderate amount of fibrosis. Dr. Stout described this as the smallest linitis-plastica type of carcinoma he had encountered up to that time.

It is my impression that, when fibrosis is marked, the inner surface of the stomach is more likely to be abnormally smooth and to resemble the rare cases of atrophic gastritis with very few mucosal folds. Its lesser curvature margin may show fine irregularities. The more the fibrosis, the more the stomach becomes diminished in size with reduced expansibility or distensibility when a barium preparation is swallowed or when air is introduced for gastroscopy. It must be emphasized that this description of this disease is inadequate. This type, even when well advanced, is the most difficult of all carcinomas of the stomach to detect and to differentiate from inflammatory changes. I have yet to see a case survive as long as five years after resection.

The unclassifiable advanced growths are, in the great majority of cases, demonstrated by roentgen-ray methods with relative ease and need no further discussion here.

Summary

The detection of carcinoma of the stomach by roentgen-ray methods, and to a certain extent by gastroscopy, depends upon two basic physical factors:

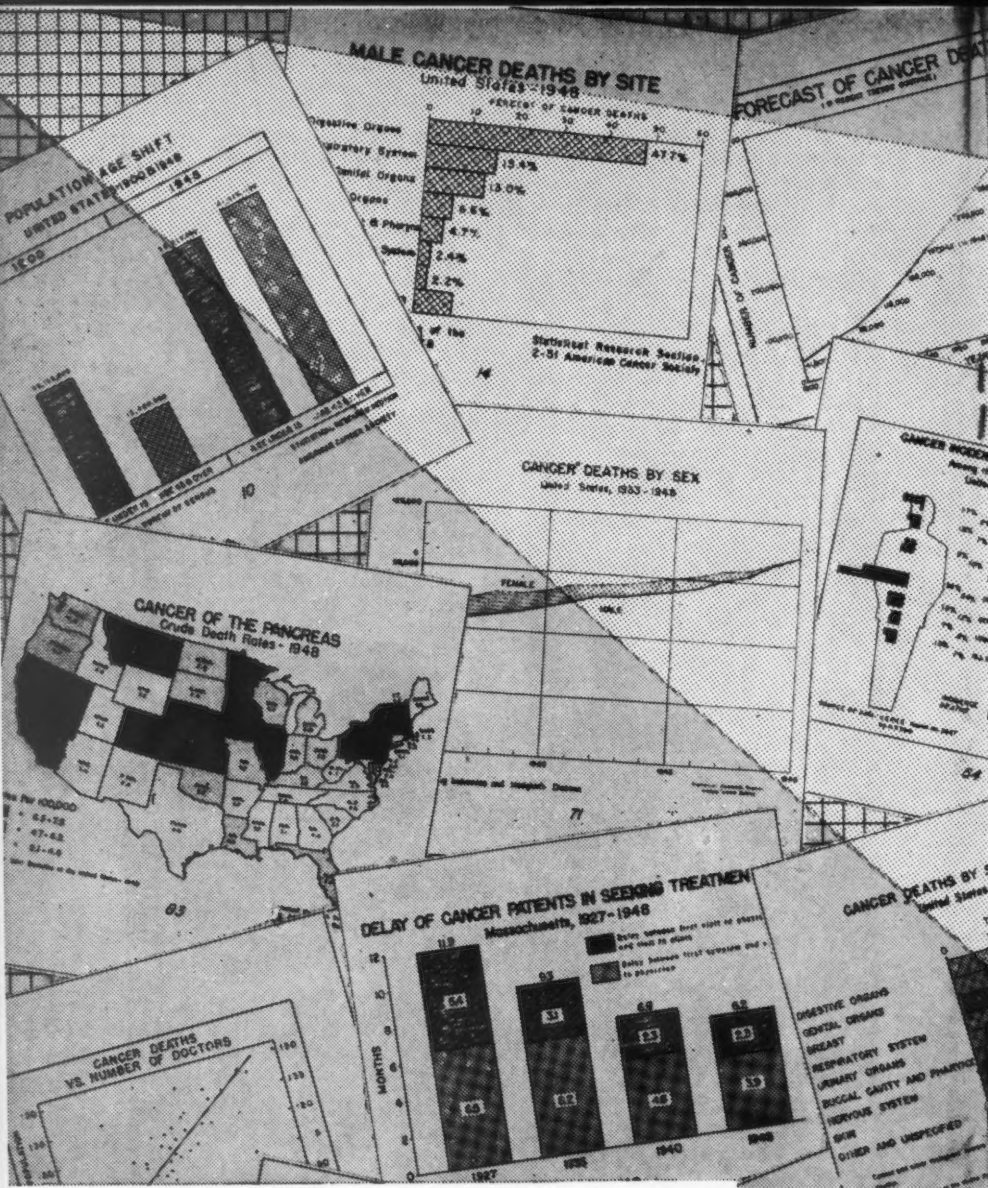
(1) the location of the growth in the stomach, and (2) the gross growth characteristics of the tumor, i.e., the physical manner in which the tumor involves the stomach wall. Stout's classi-

fication is based on this second factor and is the foundation for an understanding of the clinical evolution of this disease and of the difficulties encountered in attempting to detect it.



Figure 8. Linitis plastica type of carcinoma of the stomach. Three roentgenograms (A,B,C) are reproduced here to show (1) the remarkable flexibility of the wall manifested by deep peristaltic waves that expelled barium rapidly, and (2) the great thickening of the mucosal folds. Pressure films disclosed the appearance shown in Fig. 7, B. The gastroscopist interpreted the thickened folds of intact mucosa as evidence of gastritis. At operation extensive inoperable carcinoma was found. A biopsy of the wall, which did not go clear through to the mucosa, disclosed carcinoma cells infiltrating through the muscle without destroying it and growing along the subserosa. Very little fibrosis was present. The preservation of the muscle and the absence of fibrous tissue explain the ability of the stomach to produce deep peristalsis.





LANTERN SLIDES ON CANCER STATISTICS

See page 84 for information on how to obtain slides

CANCER DEATHS
(continued)

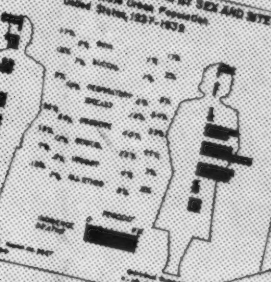
CANCER OF THE BUCCAL CAVITY Crude Death Rates - 1948



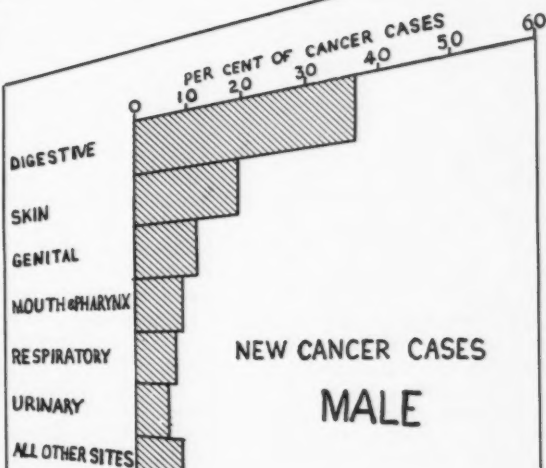
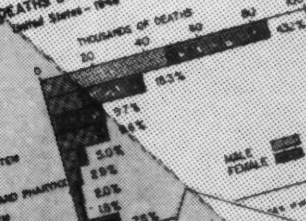
CANCER DEATHS BY SEX AND SITE United States - 1948



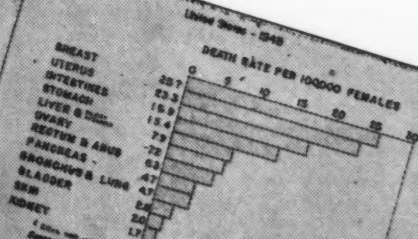
CANCER INCIDENCE AND DEATH BY SEX AND SITE Among the White United Population United States, 1937-1953



DEATHS BY SEX AND SITE United States - 1948



FEMALE CANCER



DEATH RATES BY AGE

Complications Following Radiation Therapy

Simeon T. Cantril, M.D.

To avoid complications of irradiation entirely in the treatment of the major forms of cancer is never to take justifiable risks in combating a disease process that is otherwise lethal. Nor should complications be confused with errors.

All ionizing radiation is injurious to biological media. This is a primary consideration. In therapeutic radiology we produce varying degrees of injury and, by damaging some tissues more than others, we attempt to salvage the patient. Surgery is easier to understand as are its complications. You cut out unwanted tissues and either fill in or sew up the hole, or find some other means of re-establishing continuity of function or physiology.

Radiobiology, from both fundamental studies and clinical observation, brought to us a great wealth of knowledge which serves as the basis for a sound application of irradiation to the patient. With the one possible exception of Muller's observation on the radiogenetic properties of ionizing radiation, the main avenues of experimental radiobiology were conceived and initiated by observations made in applying radiations to the treatment of disease. Experimental radiobiology as such was laboratory investigation to elucidate clinical observation. A better understanding of the mechanisms of radiation effects may lead in time to more precise and less empirical application, and, in the future, increase the ratio of the useful over the unwanted and deleterious reactions that now frequently lead to failure.

The early recognition of the differential biological action of alpha, beta, and gamma radiations from radium was a preliminary to a reasonable understanding of the effectiveness of these agents when applied to tissues.

Such early investigative work together with that defining the real importance of filtration as a means to overcome the more caustic action of otherwise unfiltered rays formed the basis for a remarkable advance in the avoidance of necrosis, both of superficial tissues when the radiation was applied externally and of deeper tissues when interstitial irradiation was used. Nor are we as yet complete in our knowledge of the differential biological action of varying forms of radiations. The advent of supervoltage roentgen rays, high-energy electron and proton beams and neutron sources opens new avenues of investigations all concerned with their specific interaction on tissues but more importantly upon their possible application to cancer. Fundamentally, such investigations must define the suitability of these radiations to the problem of the preservation of important normal structures while at the same time acting more favorably than presently available methods in the arrest of neoplastic growth.

We are indebted to the early investigators for so ardently pursuing the problem of the relative radiosensitivity of tissues. Further development has come and will continue to come by learning either (1) to alter an unfavorable radiosensitivity by biochemical or other means, or (2) to take advantage of newer developments in radiating sources that may permit a greater effectiveness with a lesser degree of important injury. The principle of fractionation and protraction, though developed early in the study of radiation effects, is perhaps one of the more neglected principles that by more careful application could overcome certain of the late complicating effects. Factors

From the Tumor Institute of the Swedish Hospital, Seattle, Washington.

that unfavorably altered the radiosensitivity of tissues received early recognition. Clinical observations on the apparent radioresistance, when they were developing in scar tissue, of otherwise radiosensitive cancers, led to the conclusion that a relative ischemia was an important factor in this altered response. An adequate blood supply seemed conducive to the maintenance of continued radiation effect. Lacking in many other refinements of present-day investigations, these early workers performed classic experiments, which supported the radiation therapist in his view that anything that enhanced or conserved adequate, circulation was important to radiation effectiveness. Anemia, infection, fibrosis, or surgical scarring were to be avoided if possible when irradiation was the agent of choice. The role of ischemia in limiting radiation response, and likewise of radiation-induced ischemia as the underlying mechanism of important complications, continually requires re-emphasis.

It is not amiss to state that every type of radiation injury, produced experimentally in animals or by casualty in man, has had a prior counterpart in misguided or unsuccessful exposure of man to various forms of ionizing radiation. Radiation carcinogenesis is such an injury and possible late complication. Much was known of this problem from past experience in radiotherapy, yet in the past decade the interest in radiocarcinogenesis has increased manifold. It would seem that this might be a grand opportunity to learn about both cancer and radiations.

One cannot leave these general considerations without acknowledging our indebtedness to the physicist in guiding us to a more precise and therefore safer use of our tools. Many of our complications, both past and present, stem from faulty concepts of the principles concerned with the problems of dose and dose distribution in normal and neoplastic tissues. The radiation therapist must be well grounded in the

natural history of cancer, the fundamental concepts of radiobiology, and the physics of ionizing radiation as it applies to distribution and dosimetry.

Broadly considered, one may think of the complications of radiation therapy as those inherent in the patient and those resulting from irradiation and the healing process.

We shall assume that the patient is host to one of the major forms of cancer that experience has demonstrated is more biologically suitable to irradiation than to other forms of therapy. It is important to appraise the general condition of the patient apart from the neoplasm and its consequences. Age, nutritional state, infection, anemia, and coexisting diseases are important considerations not only in the planning of therapy but also in the decision whether any major irradiation can be undertaken. Seldom is radiation therapy an emergency. Time should be allowed for an adequate study of the patient in preparation for treatment. The same thoroughness and clinical judgment are required in learning the extent of the neoplasm and the complications that it may already have caused. Many so-called complications of irradiation are really those of the cancer that were present at the outset and unrecognized as such.

A considerable number of the organs, which are the site of cancer and which today are treated by irradiation, are those that may develop obstruction to passage of their normal traffic. The nasal fossa, antrum, pharynx, larynx, esophagus, bladder, and cervical canal are but examples. Before starting irradiation, it is well to realize that success or failure may hinge upon the re-establishing of patency. The treatment of cancer of the bladder in the presence of prostatic or bladder-neck obstruction only invites complications from further edema and infection. The laryngeal airway close to obstruction may shortly be completely obstructed with even the most cautious approach by external irradiation. It may be more

prudent to perform a temporary tracheostomy with the hope that it may be closed following completion of treatment and reaction. Pyometria with secondary pelvic infection requires drainage. Acute tubal abscess may preferably be dealt with surgically prior to irradiation than be permitted to advance to a complication interrupting treatment. Cancer of the antrum is also a problem in necrosis and osteomyelitis and as such reacts more favorably during irradiation if debris has egress through a palatine window. Cancer of the esophagus may or may not require gastrostomy prior to therapy. This will depend on the degree of obstruction, the nutritional state of the patient, and the likelihood of reopening. If the therapy is obviously one of palliation to re-establish swallowing in a disease recognized as already beyond the confines of the esophagus, gastrostomy may defeat the aim of therapy.

A second frequent and important ally of cancer that often complicates irradiation is infection. Chemotherapy and the antibiotics have greatly reduced the morbidity from infections that formerly beset our treatment. A decade ago irradiation itself was our most important tool in nonlocalized inflammation. It still can be used effectively, but even more so with the antibiotics. The morbidity of pelvic infection in the treatment of cancer of the cervix, or the inflammation secondary to interstitial irradiation of the tongue or other parts, is now the exception rather than something always to be feared.

One other associate of cancer should be mentioned in considering irradiation. This is generalized anemia or local ischemia from the fibrosis of previous inflammation, surgery, or possibly irradiation. Anemia may be secondary to the cancer, to infection, or to blood loss. It is well to treat it in advance if possible. Ischemia of the tissues to be irradiated may in itself be a contraindication, or, if not, it may be the cause of uncontrolled cancer or of late sequelae of necrosis. One invites major

complications in treating in the presence of impaired vascularity. Radiotherapy seldom has a "second look." The impairment of vascularity secondary to irradiation closes this outlook to re-irradiation. For similar reasons, whenever surgery and irradiation are planned in combination, irradiation should precede surgery wherever possible. The irradiation of cancer of the tongue should precede surgery of the neck. If cancer of the breast is to be a combined surgical and radiotherapeutic approach, the irradiation should precede, not follow, mastectomy. Surgical fibrosis with resulting ischemia not only diminishes radiation response but seriously limits the tolerable dose to normal tissues.

In considering the complications attributable to irradiation, it may be well to examine certain of those arising during the course of treatment and those generally considered under the term of late reactions (a euphemism for complications).

The complication most commonly encountered is the one that most often begins prior to irradiation—namely radiation sickness—sometimes contracted from either the referring physician or well-meaning friends. When a patient is beset by nausea, vomiting, weakness, weight loss, or collapse attendant upon radiotherapy that is sufficiently serious to complicate the progress of treatment, there is something wrong with the therapy. Apart from attention to the general condition of the patient, nutrition, fluid intake, and rest, I am opposed to medicinal therapy of radiation sickness. Whether this be one of the vitamins, dramamine, cortisone, or a score of other suggested remedies, they serve only to mask an important guide to the conduct of therapy. Radiation sickness can be controlled if attention is given to the volume of tissue irradiated, the dose, and its spacing.

A second constitutional reaction that bears watching is the effect of irradiation upon the blood-forming tissues. When irradiating small volumes, this

may not be important. For larger volumes, frequent checks may be more prudent. Leukopenia with lymphopenia is the more usual finding. How low one may permit this depression to go depends upon many factors. If the red marrow reflects injury as well, the complication is more serious. Here again, attention to the details of treatment may be helpful, particularly in relation to volume, dose, and protraction. Blood replacement may be required if treatment cannot be interrupted. Regeneration following the completion of irradiation can be anticipated. It is only the exceptional case that requires supportive hemopoietic therapy as a result of irradiation.

Medication to control pain should be held to a minimum, otherwise it serves only to mask the effectiveness of the irradiation. Pain may result from edema secondary to irradiation and require attention to the irradiation rather than the prescribing of more analgesics. Similarly medications to counteract diarrhea used too freely mask an important sign of intestinal injury.

The recognition of impending complications before they are fully developed can only be accomplished by close clinical observation. The early observation of beginning limitation of movement of the arytenoid will precede the onset of edema and fixation or limitation of airway. Tenesmus is a warning of allowable rectal reaction, which if it progresses to a bloody mucous discharge is indicative of more serious rectal injury. In the treatment of cancer of the bladder, the severity of frequency, urgency, and spasm must be carefully judged and differentiated from infection or obstruction. In the treatment of cancers in which the mucous membranes within the field of irradiation are visible, it is important to follow and be familiar with the degrees of epithelitis associated with time-dose relationships. The problem is more complicated when one cannot observe the organ. To ignore radiation effects that are visible either directly or in-

directly, or to pass unheeded the signs of approaching tolerance to important structures, is to miss the landmarks of radiophysiology. There is always the temptation to believe that one can somehow increase the dose beyond that which experience dictates is the upper limit of eventual tolerance. With greater protraction this is possible to a limited degree. But too often the time factor is disregarded and we fall into the trap of "supralethal dose," which is synonymous with necrosis and uncontrolled cancer. We need to keep clearly in mind that anticipated biological reactions to irradiation are not in themselves complications—they are our best guide to the degree of radiation injury to both the cancer and normal tissues. To observe them closely is to keep out of major trouble both during and after irradiation.

Late manifestations of injury result from three important radiobiological effects. The one is chromosomal and may lead to carcinogenesis. The second results in atrophy, loss of function, or cellular death, of which failure of osseous development, gonadal and mucosal atrophy, and lens opacity are examples. The last is responsible for the major late complications and results from radiation-induced ischemia and fibrosis. The latter is responsible for late necrosis of bone; vesical and rectal ulcerations; stenoses of hypopharynx, esophagus, or bowel; late necrosis of skin; and a host of other sequelae. Tissues with impaired circulation do not well tolerate trauma whether inflammatory, thermal, or mechanical. Least of all, do they well tolerate major surgery, and lastly further irradiation. The management of late complications resulting from ischemia and fibrosis will vary with the anatomical location and degree of injury. Since such tissues are prone to infection, one guiding principle is directed toward the control of inflammation. In other locations, the part may be placed at rest. Hence we do not hesitate to treat the late progressive

rectal ulceration by temporary colostomy, if more conservative measures are not effectual. Late laryngeal edema may require temporary tracheostomy until cartilaginous sequestration can occur or inflammation subside. We have a patient with cancer of the hypopharynx and one with that of the esophagus who years after irradiation require periodic dilatation because of fibrosis and stenosis. This is preferable to gastrostomy. Late necrosis of bone can be more hopefully treated with antibiotics and limited surgery than formerly when an extending osteoradionecrosis was the more general rule.

The occurrence of these late and complicating sequelae is not necessarily a reflection upon judgment at the time of previous irradiation. When they occur after the treatment of advanced cancer in which one was justified in taking risks in the interest of survival they may have been unavoidable. When they arise with any frequency

otherwise, one should reappraise his entire conduct of treatment with particular scrutiny of dosimetry and protraction as well as his concept of the limitations of normal tissue tolerance.

Grid and rotational therapy have as their purpose increasing the tumor dose while reducing the injury to skin and other normal structures. Whether these be used with conventional medium voltage irradiation or with the more energetic beams, one cannot lose sight of basic radiobiological limitations of all important structures. These new tools cannot substitute for careful clinical and radiobiological observation. The same applies to the usefulness and limitations of supervoltage irradiation in whatever form.

Finally, one may avoid all major complications in radiotherapy by the expedient of never coming to grips with the performance of adequate irradiation.

King Edward VII of England was among the first to be treated with radium. He had been under treatment for a rodent ulcer of the cheek. Zinc ionization therapy had been used and abandoned after the patient was given a severe electrical shock through his necklace, a present from Maximilian, Emperor of Mexico. 22.5 mg. of radium costing £362 was spread on a flat metal surface 3 cm. square and fixed to a pair of spectacles which the King put on to read *The Times* for 20 minutes. Cure with no recurrence followed. His brother had died of carcinoma. This and his own case interested him in persuading Lord Iveagh and Colonel Ashley each to give £50,000 to found the Institute for Radium Treatment.

— Iredell, C. E.: *The early history of radium in London. Proc. Roy. Soc. Med.* 44: 207-209, March, 1951.

Influence of Sunlight on Skin Carcinogenesis

Charles R. Rein, M.D., and A. I. Weidman, M.D.

Although there are probably many causes of skin cancer, such as prolonged exposure to tar and chemicals, infection, trauma, and hereditary and endocrinological factors, one of the most important etiological agents is exposure to the actinic rays of the sun. This is corroborated by the observation of the increase in the incidence of epitheliomas in individuals less than the usual cancer age who have been exposed excessively to sunlight. Chronic exposure to the sun over a period of years leads to degenerative changes of the skin ("sailor's and farmer's skin") with its telangiectasia, keratoses, and carcinoma.

Some protection against excessive exposure to the sun is provided by nature,⁹ such as the pigmented skin of the colored races, thickness of the stratum corneum, and the furs of animals. Pigmentation of the skin could account for the low incidence of skin cancer caused by excessive sunlight in the Asiatic and African races. Hyde¹¹ in his statistical study on the prevalence of cancer of the skin in various occupations and in various geographical locations eliminated heat and frostbite as carcinogenic factors. Corson, Knoll, Luscombe, and Decker, however, reported on twelve patients in whom cutaneous changes were caused by the heat or actinic rays conducted to and concentrated on the cheeks by spectacle lenses. Of these nine proved to be basal-cell epitheliomas.

Experimentally, malignant tumors of the skin were first produced with ultraviolet radiations by Findlay (1928), who reported formation of epitheliomas in white mice after eight months of daily three-minute exposures to radiation from a mercury-vapor lamp. The active spectrum of the tumor-pro-

ducing wave lengths was between 2537 and 3200 Å. In the albino mouse, which is the most commonly used experimental animal, a large proportion of the aforementioned rays penetrate to the cutis while in the human skin only a relatively small portion of these carcinogenic rays penetrate to the cutis, the larger amount being absorbed in the epidermis. For this reason, the production of tumors of dermal origin (sarcomas), by this agent should be very rare.⁷ This would seem to explain the great preponderance of sarcomas experimentally produced in the albino mouse in contrast to carcinomas in human beings.

In this connection it is of interest to stress once more the importance of pigmentation and particularly of the thickening of the stratum corneum that follows exposure to sunlight both of which serve as protective factors against subsequent re-exposure to actinic rays. This latter is especially important in the white skin, in which the little pigment formed is an insufficient protection against the carcinogenic rays.

The following observations seem to confirm the role of sunlight in carcinogenesis:

Pigmentation of Skin

There is a definite relationship between certain characteristics of skin color and carcinoma of the skin. The factors that determine the skin color are its vascularity and pigment. Epitheliomas appear to develop less fre-

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quently in people with a dark complexion than in blondes. In the highly pigmented skins of Negroes, the large amount of pigment distributed throughout the entire epidermis provides an important protection against sunburn and perhaps against carcinoma of the skin. Epitheliomas are likewise rare in Indian farmers and in people of mixed Indian and Negro blood. The skin of the colored races is, therefore, less susceptible to sunburn and subsequent development of epitheliomas because the carcinogenic wave lengths of ultraviolet light are largely absorbed before they reach the living epidermal cells.

Color of the Eyes and Hair

A. F. Hall found that 87 per cent of a group of 100 patients with epitheliomas of the skin had eyes of light color. At least 50 per cent of the entire series were the offspring of two light-eyed parents, while the remaining had one light-eyed parent. It is suggestive that eye color has some genetic relation to skin carcinoma. In the same group, the color of the hair was investigated. Although the incidence of epithelioma of the skin was higher in people with light hair, there was no definite and conclusive evidence of "blondes" and light-haired individuals being more susceptible than brunettes to epithelioma of the skin.

Sex

This seems to be a factor as far as the incidence and the distribution of the epitheliomas are concerned. The alleged predominance of cancer of the skin in men has been attributed to the greater outdoor activity of that sex. There is a higher incidence of squamous-cell epitheliomas in male as compared with female patients, and there also seems to be no doubt that cancer of the lip occurs much more frequently in men than in women.

Occupation

It is believed¹ that cancer of the skin

occurs more frequently in outdoor workers than in those occupied indoors. The terms "sailor's and farmer's" skin applied to the aforementioned degenerative, precancerous changes in the skin, reflect the alleged connection between epitheliomas and these occupations. According to Magnusson, the incidence of skin cancer in Swedish farmers does not differ from the rest of the population. Perhaps sunlight plays a different role in carcinogenesis at different latitudes and climate. It has been pointed out, however, that mortality from cancer of the skin and lip for the United States Navy is about three times as high as for the average population of the same age group. Young and Russel credit the high occurrence of skin cancers in sailors to contact with chemical carcinogenic agents (tar and oil). Workers with coal-tar derivatives sometimes become sensitive to light and this has been connected with the occurrence of cancer of the skin among such workers. However, the importance of photosensitization in carcinogenesis is debatable.

The practical application of this discussion is the avoidance, whenever possible, of excessive prolonged exposure to sunlight by individuals with a light complexion and light eyes. The same considerations may lead to a better selection of workers in certain professions that require prolonged exposure to the sun.

Topographical Distribution

Areas of the skin most commonly affected by cancer are the exposed portions of face and extremities, the former accounting for approximately 90 per cent of all cutaneous cancers.² This point is strongly in favor of sunlight being the principal agent responsible for epitheliomas, since the face is more exposed to the sun than any other part of the body. The regions about the nose and the eyes are most frequently affected, the shaded submental area being most "immune." The relative rarity of

epitheliomas on the ears and forehead in women, may be attributable to the protective action exerted by the hair and the wearing of hats. The occurrence of an occasional basal- or squamous-cell carcinoma on an unexposed area of the body does not negate the importance of the sunlight factor, since such tumors are at times caused by other agents.

Age

Most epitheliomas appear after the fortieth year, although their occurrence at a much earlier date is not infrequent. The age at which skin cancers develop may depend on the frequency and regularity of exposure to sunlight. Experiments in mice and observation in human beings show that a few exposures, even if severe, are not likely to induce cancer of human skin. Epitheliomas seem to occur more frequently among people who are exposed regularly to the action of sunlight throughout the year than in those who develop a severe sunburn at the beach once or twice during the year. Even several repeated severe exposures are not likely to induce cancer in human skin.

Geographical Distribution

Actually, the amount of sun rays shorter than 3200 Å depends not only on the latitude but also on the amount of vapor in the atmosphere, weather, contamination with smoke and dust

that, by themselves, are able to absorb the "carcinogenic" rays. This filtering action is exerted only in a minor degree by the water vapor. High altitude is also an important factor because of the smaller amount of contaminating material in the atmosphere and because of the reduced air mass. Australian authors report a high incidence of cancer of the skin on that continent and credit that to the aridity and high altitude of many regions. Approximately 25 per cent of patients admitted to hospitals in Brisbane for carcinomatoses have the cutaneous type. According to American statistics, the incidence of cancer of the skin in Atlanta is three to four times as great as in Chicago. It is difficult to establish here whether the greater incidence of skin cancer in the South is due to the larger amount of carcinogenic rays or because the mildness of the climate permits more time outdoors.⁴ The statistical data show also that cancer of the skin and lip in the United States Army and Navy occurs much more frequently among those born and raised in the Southern States than among those born in the Northern States.

Conclusions

1. It appears quite evident that excessive chronic exposure to sunlight is an important contributory factor in the development of skin cancer.
2. Several facts that confirm the carcinogenic action of sunlight are discussed.

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Case N-114270. (X-ray No. 187325. Pathology No. 52-989)

A 50-year-old Anglo-Saxon janitor, complaining of difficulty in swallowing, is referred to the Tumor Board by his family physician.

The patient has had difficulty in swallowing solid foods for nine months, without pain or loss of appetite. His voice is hoarse but he insists that this has been present for ten years. His current weight is 113 lb.; weight one year ago, 125 lb. The patient has had no major operations or previous radiotherapy.

Physical Examination. The head is negative. The neck reveals no palpable nodes. The jaws are edentulous. Examination by mirror shows a mass, 3 cm. in diameter, involving the right side of the epiglottis, the right vallecula, and apparently the base of the tongue. There is some thickening of the right false cord and arytenoid, but the true cord moves freely (Fig. 1).

The chest shows the lungs clear; heart, regular rhythm and no murmurs. The abdomen contains no palpable masses. Rectal examination is negative. The extremities are negative.

Laboratory examination shows: Hb, 12 gm.; Wassermann, negative; urine, negative; white blood count, normal.

Roentgen-ray examination shows no evidence of metastasis in the chest. There are old fractures of the right third to seventh ribs. Soft-tissue studies and laminograms of the neck show a mass involving the right side of the epiglottis and vallecula; there is slight edema of the right false cord. The roentgenograms were demonstrated by the radiologist (Dr. M. A. Sisson). (Figs. 2, 3).

PATHOLOGICAL EXAMINATION. Biopsies were taken from the upper edge of the epiglottis, the posterior surface of the epiglottis, and the base of the tongue. The first biopsy showed no evidence of tumor; the others showed poorly differentiated squamous-cell carcinoma (Fig. 4).

The patient was presented by his attending physician and examined before

From the Consultative Tumor Board, Stanford University Service, San Francisco Hospital, San Francisco, California. Submitted by L. H. Garland, M.D., Secretary and Moderator, Stanford Tumor Board.

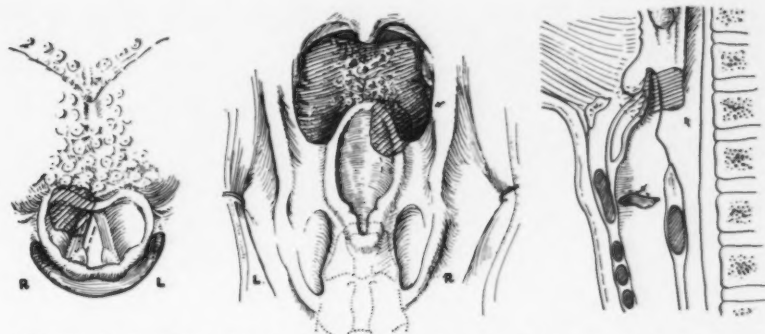


Figure 1. Diagram showing approximate location and extent of the tumor. Squamous-cell carcinoma of epiglottis, extending to vallecula, and probably to portion of base of tongue. Clinical stage 2.

the Tumor Conference. He is in fairly good physical condition. No definite cervical nodes are palpable. Clinically there is a stage-2 carcinoma of the epiglottis, with probable extension to the base of the tongue.

Discussion

SURGEON (Dr. C. Mathewson): This man has an extrinsic carcinoma of the larynx, involving the epiglottis and probably the right side of the base of the tongue. The mass is localized and

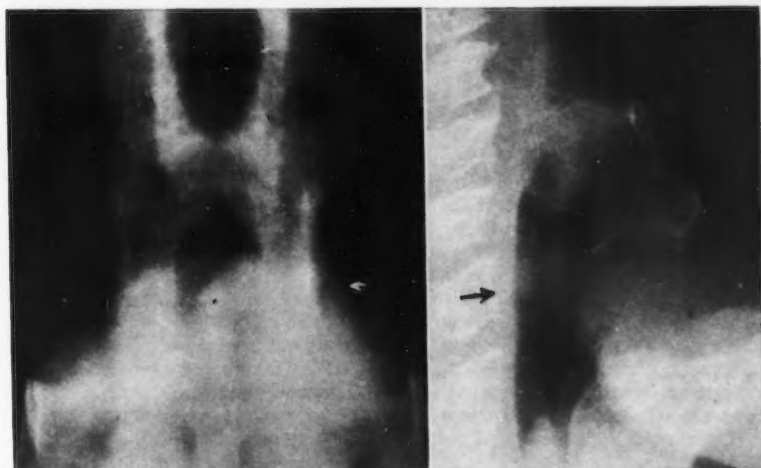


Figure 2. Figure 2 shows the lateral roentgenogram of larynx and antero-posterior tomogram of larynx. In the lateral roentgenogram the bulky soft-tissue mass involving the upper third of the epiglottis is well seen. In the tomogram the soft-tissue mass involving the right half of the superior portion of the epiglottis displaces the adjacent air shadow. There is slight swelling of the right false cord probably owing to edema.

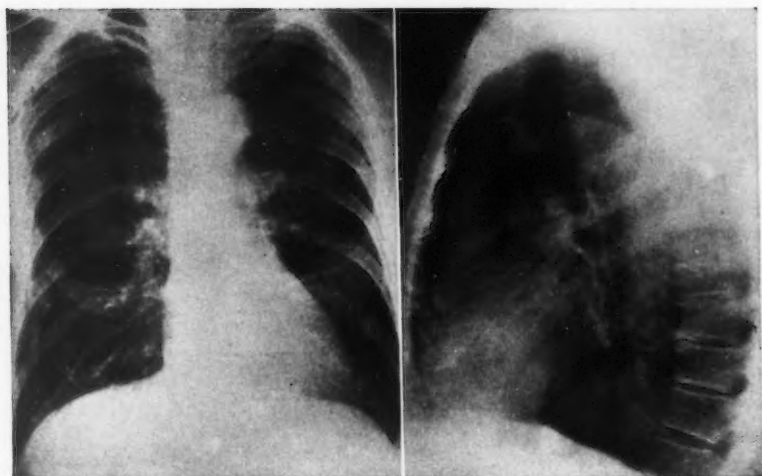


Figure 3. The posteroanterior and lateral roentgenograms of chest reveal no roentgenographic evidence of metastasis.

could be excised with the regional nodes en bloc. However, the patient would have to undergo removal of most if not all of the tongue, together with the larynx, if this were attempted. Under these circumstances it is my recommendation that radiotherapy be used.

OTOLARYNGOLOGIST (Dr. S. Christerson): There is some difference of opinion regarding the operability of this lesion; on the whole I believe it is inoperable. I recommend radiotherapy.

RADIOLOGIST (Dr. L. H. Garland): The patient has an exophytic lesion in a relatively accessible site; it should be possible to deliver a curative dose of radiotherapy to this region, with a reasonable chance of cure. I concur in the recommendation of radiotherapy.

QUESTIONS* Will not a heavy dose of radiotherapy be followed by chondronecrosis?

ANSWER: In the case of the epiglottitis, it is probable that curative therapy can be given with very slight chance

of late chondronecrosis. The reason is that the diseased portion of the epiglottis will shrink or slough off at the termination of the course of therapy. It is a different matter when the arytenoid or thyroid cartilages are invaded by secondary infection; in these sites, radical radiotherapy carries a definite chance of late chondronecrosis when infected cartilage has been heavily treated.

QUESTION: In view of the large mass shown by roentgenography should not the patient have a tracheostomy?

ANSWER: No. The initial doses of radiotherapy will be small and the patient will be watched closely. It is preferable to attempt completion of the course of treatment without tracheostomy if such can be avoided.

QUESTION: Should the patient have bilateral neck dissection; the pathologist has reported the lesion to be a poorly differentiated carcinoma?

ANSWER: In the absence of palpable cervical nodes, it is believed best to observe the patient at frequent intervals following his course of radiotherapy—and to defer consideration of radical

*Questions were from visiting staff members and house staff; answers were by moderator and other Tumor Board members.

operation on the neck nodes until and when there is clinical evidence of neoplastic adenopathy, that is, assuming that the primary tumor is arrested. This is our policy at the present time.

QUESTION: If radiotherapy is not successful what is the plan?

ANSWER: Radical surgical removal. However, a period of at least two months will be allowed after termination of radical radiotherapy, before considering this aspect of the problem. Some tumors, especially in this location, are slow in shrinking, at least initially. We have had a few that did not entirely disappear for as long as three months after treatment, but which then remained arrested for more than five years.

QUESTION: If radiotherapy is to be used, should it be in the form of supervoltage or radium therapy?

ANSWER: The most flexible and clinically useful type of radiotherapy for lesions of the neck is 200 or 250 kv. roentgen-ray therapy. Supervoltage or radium-beam units are unwieldy and have not been shown to give results superior to those obtainable with properly employed 200 kv. roentgen-ray beams. We propose to use "orthovoltage" therapy.

QUESTION: What is the prognosis?

ANSWER: Radical radiotherapy gives about 40 per cent five-year arrests in tumors of the free border or upper one third (the suprahoid portion) of the epiglottis. However, the element of extension to the vallecula and probably the base of the tongue in this particular case renders the prognosis less favorable.

The Tumor Board recommended radiotherapy. The patient was referred

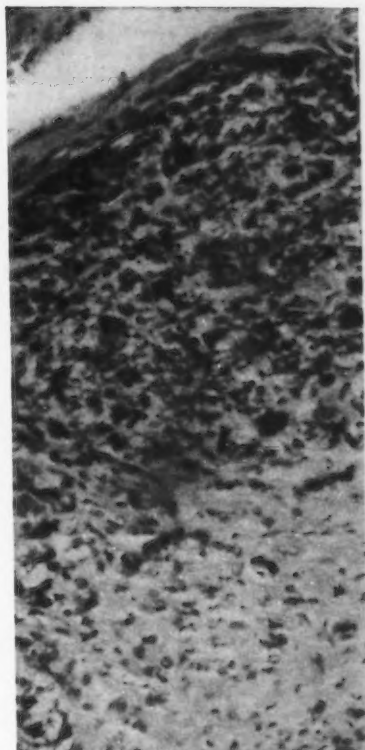


Figure 4. Photomicrograph showing somewhat poorly differentiated squamous-cell carcinoma. This biopsy was taken from the posterior portion of the soft-tissue mass involving the epiglottis.

to the radiological service for care. He will be presented again following treatment, and at periodic intervals thereafter.

Rutherford devised very ingenious methods for measuring various fundamental quantities connected with this subject and obtained very valuable results which helped to make the subject metrical whereas before it had only been descriptive.—J. J. Thompson: Rutherford.

A Standardized Method for Reporting Cancer End Results

The lack of uniformity in reporting cancer end results has been a source of worry to clinicians and research workers seeking to evaluate therapy from published reports. In order to overcome this difficulty, the Joint Committee on Reporting Cancer End Results was established to recommend rules and forms aimed at eliminating the major causes of confusion. The Committee was composed of representatives of the American College of Surgeons, the College of American Pathologists, the American College of Radiology and the American Cancer Society with the addition of one member-at-large from the National Cancer Institute. The following report was adopted by the Committee.

The purpose of any statistical analysis is to obtain reliable answers to certain specific questions. Therefore, the analytic method of choice depends upon the nature of the questions as well as upon the data available and it is frequently necessary to employ several different methods in order to answer various questions. For this reason, no one method of analyzing cancer end results can be recommended as a solution to all the problems which may arise. Nevertheless it is possible to outline certain basic principles and to suggest a simple standard type of analysis applicable to most sets of data on this subject. More detailed supplementary analyses would then depend upon the exact problem which the investigator seeks to elucidate.

The following are among the most common of the numerous reasons for reporting cancer end results:

- 1) Comparison of the effectiveness of alternative methods of treatment
 - a) in achieving permanent cures,
 - b) in extending the life of the patient whether or not permanent cures are achieved,
 - c) in recurrent

cases of cancer, d) in the relief of suffering in incurable cases of cancer.

- 2) Analysis of the influence on the course of the disease of such factors as a) histologic type, b) size and extent of the lesion, c) evidence of metastasis, d) duration of symptoms, e) age and condition of patient.

While there are various perfectly correct methods by which these comparisons may be made, it is obvious that two different series of cases can be compared only if the same method of analysis is used for both. For example, the effectiveness of a certain treatment used by one doctor can be compared with the effectiveness of an alternative method of treatment used by another doctor only if the end results are presented in exactly the same way. Thus a standardized method of reporting is essential when the purpose of reporting is to make such comparison possible. This in no way limits the freedom of the investigator to make additional analyses by other or more detailed methods when desirable.

A great deal of confusion exists in the reporting of cancer end results. Widely different cure rates are published for what appears to be the same type of cancer and it is frequently impossible to tell whether the differences are due to variation in the method of treatment or whether they are due to variations in the method of reporting end results. The principal reasons for this confusion seem to be:

- a) *Selection of cases.* The result of therapy depends in no small measure upon the condition of the patient at the time the treatment is initiated and there are great variations in the type of patients coming to the attention of different doctors. For example, some doctors see a

preponderance of advanced or recurrent referred cases while other doctors see a preponderance of relatively early cases and refer their advanced cases for treatment elsewhere. Aside from this there is frequently a selection in the cases reported in the literature. Some authors present only "hopeful" cases, some present all cases treated (whether hopeful or not), and some present all cases seen (including those not treated).

- b) *Proof of diagnosis.* Some authors present only cancer cases with microscopic confirmation of the diagnosis, some include cases without microscopic confirmation of the diagnosis, and still others simply make no mention of the method of diagnosis.
- c) *Inadequate follow-up.* Comparatively few doctors or hospitals are able to obtain a five year follow-up on every diagnosed case of cancer. Survival rates are usually based only upon those cases which were followed, but frequently no mention is made of the number of cases which were lost to follow-up. This also can make a considerable difference in survival rates since it cannot be assumed that untraced cases had the same history as traced cases. From our observations, it appears that the proportion of cases followed for five years varies from 100% down to a very low percentage indeed.
- d) *Cure rates vs. survival rates.* "Five year cancer cures" are distinguished from "five year cancer survivors" by the fact that the former are cases which are alive and apparently free of cancer five years after diagnosis, while the latter are all cases alive five years after diagnosis including cases alive but with evidence of cancer. While both five year cure rates and five year survival rates are useful (though for somewhat different purposes) serious error results from mislabeling or failure to

specify clearly which of the two is meant. Another difficulty which arises in this matter is the fact that in reporting five year cure rates there has been no uniform method of handling cases which die of causes other than cancer before the end of the five year period.

The rules and standard forms adopted by the Committee are given at the end of this report. They are designed for the presentation of minimum basic information in a uniform manner. It should be emphasized that the investigator is expected to give additional information in supplementary tables and in the text. This will give the reader the necessary data to make analyses most suitable for the purpose he has in mind. For example, the reader will be able to compute five year cure rates or five year survival rates as he sees fit. In some instances, an author may wish to supplement his report with information on yearly results up to and beyond the five year period.

Certain problems in connection with the use of the standard form should be clarified. In reporting on a series of cases, a form should first be filled out including every case seen of the particular site or type under consideration. The series should be precisely identified in terms of site, source of cases, and time period covered. Supplementary forms may then be filled out for selected subgroups classified according to such factors as stage, grade, histologic type or method of treatment.

The general summary section at the top of the form need only be filled out for the overall series of cases. It is included to insure that all cases are reported without selective bias. The total experience is divided into four mutually exclusive categories: Section A, Section B, Other (a), and Other (b). Those cases classified as "Other" appear only in the summary; whether or not these cases had been treated previously is immaterial and no follow-up information is required on them.

Membership of the Joint Committee
on Reporting Cancer End Results

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Health Service

RULES FOR REPORTING FIVE-YEAR END RESULTS OF PERSONS WITH
MALIGNANT NEOPLASTIC DISEASES

1. Include *all* cases diagnosed as having a malignant neoplasm, whether treated or not. Whenever possible, all cancers should be classified according to the site of origin.
2. Cases reported should be divided into two Sections, A and B, as defined below.
Section A. *Cases not previously treated.*
The duration of these cases is measured from the date of the original diagnosis of this cancer.
Section B. *Cases previously treated.*
The duration of these cases is measured from the beginning of subsequent treatment.
The total number of cases in Section A and the total number of cases in Section B should always be reported. However, if the investigator so desires, he may report the full details for one of these two Sections only. It is generally desirable to report every case from the date of original diagnosis until the end of the five year period. If this is done, then all cases will fall in Section A. The detailed tabulation of Section B cases is designed primarily for those investigators who wish to report on the efficacy of treatment in recurrent cases of cancer.
3. Include only cases with an elapsed duration of at least five years. Report the status of each patient on the fifth anniversary. Each patient should be examined at least yearly.
4. The condition of patients classed as alive and free from cancer must be established through examination by a physician at the end of the five year period or a later date.
5. The percentage of cases with a microscopically confirmed diagnosis is a measure of the accuracy of diagnosis. This percentage should be as high as possible; however, cases without microscopically confirmed diagnosis should be included but shown separately.
6. Whenever possible, an autopsy should be performed. A high degree of accuracy requires that autopsies be performed at least on all those patients who die before the end of the five year period.
7. The percentage of cases untraced for the full five years should be as close to zero as possible. If it is greater than ten percent, the report will be of doubtful validity.
8. In reporting on cancer of a given primary site, patients will be classified according to the status of that disease. If a new primary histologically proven cancer de-

velops, it should be considered as an intercurrent disease even though it may cause the death of the patient.

9. It is most important that the report should include all the basic data shown on the accompanying forms. This is considered to be the minimum amount of information needed for a useful report; many

investigators will wish to give additional information in supplementary tables and in the text. It is left to the discretion of the investigator whether he wishes to compute five year survivor rates or five year cure rates or both.

10. The attached form is recommended for use in tabulating end results.

A REPORT OF FIVE YEAR END RESULTS

October 1951

CANCER OF

This series consists of all patients with cancer of the, both early and advanced, applying to during the period to

GENERAL SUMMARY		Number of Cases
TOTAL EXPERIENCE—All patients applying		
SECTION A	Cases not previously treated	
SECTION B	Cases previously treated	
OTHER	a. Applied after treatment elsewhere, no evidence of cancer on admission or thereafter	
	b. Consultation only, no treatment requested	

SECTION A. Cases not previously treated

RESULTS AT END OF FIVE YEARS		Number of Cases		
		With Microscopic Proof	Without Microscopic Proof	Total
GROUP I	c. Refused proffered treatment			
	d. Untraced for full five years without recurrence at last examination			
GROUP II	e. Dead within five years of other causes without recurrence of cancer			
GROUP III	f. Dead, cancer present or died of complications of treatment			
	g. Dead—presence of cancer unknown			
	h. Living with cancer present at 5 years			
	i. Living with condition unknown at 5 years			
	j. Untraced full five years with cancer at last examination			
	k. Untraced full five years, not classifiable in "d" or "j"			
GROUP IV	l. Living, continuously free of cancer, verified by medical examination at 5 years			
	m. Living, apparently free of cancer, not verified by medical examination at 5 years			
	n. Living, successfully treated for recurrence, free of cancer at 5 years			
TOTAL				

(Section B on following page.)

SECTION B. Cases previously treated

RESULTS AT END OF FIVE YEARS		Number of Cases		
		With Microscopic Proof	Without Microscopic Proof	Total
GROUP I	c. Refused proffered treatment			
	d. Untraced for full five years without recurrence at last examination			
GROUP II	e. Dead within five years of other causes without recurrence of cancer			
GROUP III	f. Dead, cancer present or died of complications of treatment			
	g. Dead—presence of cancer unknown			
	h. Living with cancer present at 5 years			
	i. Living with condition unknown at 5 years			
	j. Untraced full five years with cancer at last examination			
	k. Untraced full five years, not classifiable in "d" or "j"			
GROUP IV	l. Living, continuously free of cancer, verified by medical examination at 5 years			
	m. Living, apparently free of cancer, not verified by medical examination at 5 years			
	n. Living, successfully treated for recurrence, free of cancer at 5 years			
TOTAL				

Lantern Slides on Cancer Statistics, pages 66-67, illustrates a few of the slides on cancer statistics that are available for loan in either the standard ($3\frac{1}{4} \times 4$ in.) or the small (2×2 in.) size.

A catalogue of slides available for loan can be obtained from

The Statistical Research Section
 Medical and Scientific Department
 American Cancer Society, Inc.
 47 Beaver Street, New York 4, New York



DOCTORS' DILEMMAS

Q *It is true that the incidence of leukemia is much greater among radiologists than among nonradiological physicians and surgeons? Is this attributed to the radiologist's "occupational hazard" of exposure to ionizing radiation?*

A Over a twenty-year period leukemia occurred more than nine times as frequently among radiologists as in their colleagues in other fields of medicine. Exposure to ionizing radiation, experimentally, has been shown to increase the incidence of leukemia in mice, and one is probably justified in assuming a similar hazard following exposure for men.

Q *When pathological examination of frozen sections fails either to eliminate or to confirm a diagnosis of cancer of the breast, is it justifiable to close the wound and await the pathologist's report on paraffin sections?*

A Actually, it is only infrequently that frozen sections will not provide a definite diagnosis of breast lesions. Sometimes papillary growths situated at a distance from the subareolar area of the breast are confusing, and it is difficult to distinguish papillary cancer from papilloma. One does not, of course, advocate delaying operation when it can be performed at once, but studies of a series of cases of cancer of the breast in which there was a delay

of from one to ten days between biopsy and radical mastectomy indicated that final results were not worse than in cases in which immediate operation was performed. When a pathologist is not available to interpret frozen sections, or when frozen sections do not yield a definite diagnosis, the surgeon can only excise tissue for biopsy and await the pathologist's report on the paraffin section. To proceed with radical mastectomy in the absence of histopathological confirmation of the diagnosis is rarely justifiable.

Q *What findings might lead to earlier diagnosis of cancer of the pancreas? A patient who had complained of vague abdominal aches and pains for a period of eight months, which he attributed to "chronic appendicitis" finally persuaded a colleague in another hospital to operate. On exploration, a tumor involving the body of the pancreas was found. While under my care, several careful physical examinations were done; blood studies were normal and three gastrointestinal series disclosed no abnormalities. The patient was considered neurotic. In retrospect, I believe that over the months a mental depression of mild proportions developed progressively in this patient.*

A It has recently been reported that progressive and noticeable mental depression has been noted associated with

cancer of the pancreas, but an adequate explanation for this finding has not been advanced. Cancer of the pancreas usually has as its only warning the complaint of abdominal pain. Any abdominal pain, mild, moderate or severe, constant or intermittent, in any part of the abdomen, when it is of recent origin, (frequently associated with unexplained weight loss) must be promptly and thoroughly investigated. Since there is no diminution in pancreatic secretion early in the disease, there are frequently no other symptoms than those noted above, and when physical examination x-ray studies, and laboratory findings are negative, a tentative diagnosis of possible cancer of the pancreas must be considered. Diagnostic laparotomy should not be delayed if these patients are to have a chance for survival.

Q *I have heard the statement that a persistent, asymmetrical enlargement of cervical lymph nodes in an adult is almost always an indication of malignant disease. Is this correct?*

A Yes. When asymmetrical enlargement of cervical lymph nodes occurs in an adult it is almost invariably associated with a malignant process and most frequently is due to metastases from a primary lesion in the mouth or pharynx—occasionally from a viscus below the level of the clavicle. Cervical metastatic cancer is the most frequently encountered type of malignant neoplastic disease in this anatomical location in adults, and no other diagnosis should be made except by exclusion of

this probability. In children, asymmetrical enlargement of cervical lymph nodes MAY be due to metastatic cancer, but the probability is much less likely than it is with adults.

Q *What type of moles, occurring in adults, should be excised because of their potentially malignant characteristics? I have recently had several requests from patients with what appear obviously benign moles to remove the moles, not for cosmetic reasons, but because the patients have learned that "a cancer can develop from a mole."*

A In general, all pigmented moles that occur on the soles of the feet, the palms, or the genitalia must be presumed clinically to be junctional nevi, compound nevi, or melanocarcinoma and should be removed, since melanocarcinoma of the skin or mucous membranes is presumed to arise from junctional or compound nevi.

The intradermal nevus, which is the common mole, probably does not undergo cancerous change. Such benign intradermal nevi do not occur, or do so with exceeding rarity, on the palms, soles, or genitalia. The intradermal nevus may be any shade of brown and smooth, papillary, or hairy. The presence of hair in a pigmented lesion is strong presumptive, but not conclusive, evidence that the lesion is an intradermal nevus.

Obviously, any nevus subjected to continued irritation or trauma (belt line, shoulder-strap area, on the face where it is cut in shaving) would best be removed.

No man can explain directly to another man *how* he does any one practical thing, the doing of which he himself has accomplished, not at once, or by imitation, or by teaching, but by repeated personal trials, by missing much, before ultimately hitting. . . . *John Brown* (1810-1882) in "The Art of Diagnosis."



new developments in cancer

Control Intractable Pain . . .

Intractable pain, a common consequence of head and neck cancers, has been controlled completely in six patients experimentally treated with frontal lobe injections of procaine at the University of Pennsylvania Hospital. Grant and Nulsen found that the injections gave rapid and lasting relief and constituted, in effect, a "chemical lobotomy." The patients acknowledged being aware of the existence of pain, but they asserted that they were not distressed by it. More important, anticipation of pain and anxiety were banished; and all patients were able to view their medical hopelessness and inevitable ends with serene objectivity. Current experiments are designed to calculate the duration of relief per unit of drug. Some injections afforded relief for weeks. Second injections were more effective than the first.

Radiogold and Prostate . . .

Flocks and others (State University of Iowa) have injected radiogold interstitially into 160 prostatic cancers during the last twenty months and have achieved apparently complete (but possibly temporary) remissions in

about one half the cases. The deadly golden flood destroys not only the primary tumors but in some cases is borne (by macrophages?) along lymphatics to attack nearby points of spread. Differential uptake by the cancer cells favors normal prostatic tissue; but dosages must protect bladder, rectum, and other neighboring sensitive structures. Distant metastases are unaffected by radiogold.

Single Cancer Cell . . .

The possibility that a single cancer cell may be more deadly than an entire clump of them is being explored by Hauschka (Institute for Cancer Research, Philadelphia). He has been growing single ascites cells in hanging drops to produce genetically pure clones for his experiments. Preliminary experiments indicated that four or five cells—some of them damaged in handling—were thoroughly able to produce more rapidly growing tumors than those developing from standard transplants. Now he is injecting animals with single cells—he knows they are single cells because he can count them in pipettes under the microscope—to test their takes. It is conceivable that clusters of cells that are genetically dif-

ferent may contain a common antigen that would stimulate vigorous antibody reaction, whereas a single cell may stir a slighter immune response.

Estrogen Excretion . . .

Nathanson and Engel (Massachusetts General and Harvard) have found that androgens given to breast and prostatic-cancer patients are excreted as estrogens. Chemical, even commercial, synthesis of estrogen from androgen is feasible. But this is the first time that the alterations have been detected in nature. The results resurrect an old and highly speculative idea—but this time with some basis of proof—that the normal or abnormal system is capable of transforming one sex hormone into another. These are among the early observations of techniques (counter-current distribution, chromatography, and lysis by enzymes) recently perfected and now being applied to urinary studies of patients.

Terramycin Warning . . .

Klopp and others (George Washington) have reported that terramycin in large doses may be dangerous to debilitated patients. Eight of ten advanced cancer patients seem to have died prematurely after large (but, according to the literature, safe) doses. Studies showed they developed pronounced lethargy, avid thirst, and a shocklike condition. Blood levels of the drug continued to rise with each succeeding dose. Terramycin was used in line with experimental antibiotic treatment of terminal patients. The George Washington team have achieved very good results against some cancers with aureomycin and radiation.

Infrared Snapshots . . .

The simple technique of making infrared snapshots has shown up some cases of breast cancer in experiments at Marquette. Massopust, the photog-

rapher, has made pictures of the breasts of 1600 cancer suspects, found seventy cases of cancer and missed four. Determinations were based upon the vascular patterns that are brought out clearly on infra red film (the rays penetrate the skin about 2 mm.). Interrupted or engorged veins indicated cancer. Regular photographic equipment plus an infrared filter and film were used.

Myeloid Metaplasia . . .

Experience by Block and Jacobson (Chicago) indicates that many (20 to 50 per cent) patients diagnosed as having hopeless and malignant chronic myelogenous leukemia may have non-malignant myeloid metaplasia, which offers a life expectancy of ten to thirty years. Moreover, some of the measures taken to manage the leukemia (radiation and splenectomy) may terminate the lives of myeloid-metaplasia patients within a few months. The studies showed that every case diagnosed as leukemia following polycythemia vera was, in fact, myeloid metaplasia. The scientists have reported that one sure method of differential diagnosis is spleen biopsy.

Adrenalectomy . . .

Huggins (Chicago U.) notes these results after eighty bilateral adrenalectomies: about one half the cases of cancer of the breast and prostate—no other types so far—are benefited by the operation. Patients can be maintained satisfactorily with small daily doses of cortisone. Ovariectomized and adrenalectomized patients who were not helped continue to excrete estrogen products. These results suggest that traditional concepts of the sources of adrenal hormones and estrogen be re-examined. Some of the white-haired male patients developed iron-gray hair following adrenalectomy; and many of them reported losing their habitual anxieties and angers.

mortem disclosed the pituitary had been removed completely and lesions, primary and metastatic, had regressed perceptibly.

Baker (Chicago U.) has found that colon bacteria frequently cause infection of ureter transplants (following bladder removal), stricture, and fatal kidney disease. In more than a score of patients these consequences were prevented by giving the patients cortisone at the time of operation.

Carruthers (Wash. U.) has found a pyridine-like compound in epidermis that appears not to be present in any other tissue, including skin cancers. It disappears as cancer comes.

Puck (Col. U.) has identified at least some of the chemical groups responsible for the physical attachment of virus (phage) to cells (E. coli). Environmental ions produce unlike charges (negative carboxyl and positive amino groups) that make attachment possible. In distilled water, virus and cell surfaces normally are negative and repellent.

Wilkins (Hopkins) now has twenty-three pseudo-hermaphrodites (from congenital adrenal hyperplasia) under treatment with small daily doses of cortisone. All have assumed true sex characteristics. When five were taken off cortisone for a few weeks, all five showed signs of relapse. Cortisone was resumed and symptoms disappeared.

The unique opportunity of studying the preleukemic phase of adult acute leukemia has been seized upon by Block and Jacobson (Chicago U.). A dozen patients -- including ten women anywhere from one to twenty years past the menopause -- were under observation for from three to thirty months before leukemia developed. Preleukemic symptoms resembled the blood and organ response to repeated injury or infection, cycles of organic atrophy and regeneration -- and, finally, overregeneration. All patients had multiple allergies. Six more possible preleukemics now are being observed.

Fink (Col. U.) and Snell (Jackson Memorial Lab.) are exploring antibody production by animals given homologous tumor transplants. In first tests, they have sensitized one mouse strain against a common tumor and noted no or few tumor takes on later transplant. They are now attempting to isolate and identify the antigen or antigens.

Mayer (Hopkins) has evidence that antibodies may

not have to attack an antigenic cell at hundreds of thousands of points. One good vulnerable point may be enough, according to his preliminary evidence.

Witschi (U. Iowa) has discovered that if 2 mg. of estradiol are given in water to polliwogs, the adult adrenal is ten times normal size and effects are noted in other glands. The results raise the question: Could a high concentration of maternal estrogen during pregnancy cause the fetus future adrenal hyperplasia and possibly adult cancer (of the breast and cervix).

Luyet (St. Louis U.) a veteran in freeze-drying studies, has found no perceptible chemical differences between cancer and normal cells; but he suspects they are there. Cancer cells have been reported to withstand freezing better than normal cells. Luyet has found that antifreeze compounds -- like rapid-freezing -- protect cells against crystallization processes incurred in relatively slow freezes. Cancer cells seem to survive freezing even in the absence of outside antifreeze. Do cancer cells produce their own glycerol or other antifreeze compound? That's Luyet's current big problem.

Fishman's (Tufts) studies on beta-glucuronidase levels in blood, tissues and urine are reaching the point where they may indicate why sex hormones are effective in some individuals and not in others. He has found distinct genetic differences of kidney glucuronidase synthesis in mice of five strains. Hormone effect seems to be correlated with glucuronidase production.

The intriguing studies of ageing and carcinogenesis by Lansing (Wash. U.) have moved another step forward. He found earlier that normal cells lost their free and bound calcium as cancer developed and thus assumed one of the properties of young cells. Now he has discovered that a thin layer of ribonucleoprotein is associated with the cell surface, and that if it is knocked out (with ribonuclease) calcium uptake by the cell is inhibited.

Homburger, Rietton, and others (Tufts) have tested a couple of European cancer "cures" -- and found them wanting. An antitumor organ extract (an ether suspension of fat that could not be properly diluted) from Italy proved too dangerous for use in humans. Mycetin d'Angellis, a bacterial antibiotic from infected cat granuloma, produced chills, fever, and other severe reactions in patients but had no effect on their tumors or those of mice.

COMING MEDICAL MEETINGS

Date	Association	City	Place
1953			
April 9-11	American Association for Cancer Research	Chicago	Drake
April 13-17	American College of Physicians	Atlantic City	Convention Hall
April 21-23	Ohio State Medical Association	Cincinnati	Netherland-Plaza
April 21-24	Industrial Medical Association	Los Angeles	Statler
April 26-29	Texas Medical Association	Houston	Shamrock
April 27-30	Connecticut State Medical Society	Hamden	Hamden High School
April 28- May 1	Philadelphia County Medical Society	Philadelphia	Bellevue-Stratford
May 2-4	American Society of Clinical Investigation	Atlantic City	Steel Pier
May 4-8	New York State Medical Society	Buffalo	Statler
May 10-13	Medical Association of Georgia	Savannah	De Soto
May 11-14	American Urological Association	St. Louis	Jefferson
May 18-20	Minnesota State Medical Association	St. Paul	Auditorium
May 18-20	Medical Society of New Jersey	Atlantic City	Haddon Hall
May 19-21	Massachusetts Medical Society	Boston	Statler
May 19-22	Illinois State Medical Society	Chicago	Sherman
May 24-27	California Medical Association	Los Angeles	Biltmore
May 28-31	American College of Chest Physicians	New York City	New Yorker
June 1-5	American Medical Association	New York City	Grand Central Palace
June 7-10	Northeastern Dental Society	Swampscott, Mass.	New Ocean House
June 10-13	American Proctologic Society	Boston	Statler
June 14-18	American Society of Medical Technologists	Louisville	Brown
June 15-19	Canadian Medical Association	Winnipeg	Royal Alexandra
July 14-25	International Congress of Radio-Biology	Copenhagen	
July 19-25	International Congress of Radiology	Copenhagen	
July 20-22	Postgraduate Medical Assembly South Texas	Houston	Shamrock

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